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REVIEW ARTICLE
Causality in acute encephalitis: defining aetiologies

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SUMMARY

Defining the causal relationship between a microbe and encephalitis is complex. Over 100 different infectious agents may cause encephalitis, often as one of the rarer manifestations of infection. The gold-standard techniques to detect causative infectious agents in encephalitis in life depend on the study of brain biopsy material; however, in most cases this is not possible. We present the UK perspective on aetiological case definitions for acute encephalitis and extend them to include immune-mediated causes. Expert opinion was primarily used and was supplemented by literature-based methods. Wide usage of these definitions will facilitate comparison between studies and result in a better understanding of the causes of this devastating condition. They provide a framework for regular review and updating as the knowledge base increases both clinically and through improvements in diagnostic methods. The importance of new and emerging pathogens as causes of encephalitis can be assessed against the principles laid out here.

Key words: Aetiology, case definition, encephalitis, infection.

INTRODUCTION

Encephalitis is a complex syndrome of multiple aetiologies and pathogeneses. The clinical diagnosis of encephalitis is complicated as the symptoms and signs are similar to many other serious neurological diseases. Infection is the commonest cause of acute encephalitis where an aetiological diagnosis is made; however, in most cases the cause remains undetected [1]. When an infection is detected in a patient with encephalitis, another complexity presents itself: with what certainty can we say the infectious agent is actually causing encephalitis? In 1890 Robert Koch described a series of conditions that must be met to establish a microorganism as the cause of a disease and additional criteria were added later by Rivers for virus infections; however, not all microbes associated with encephalitis can be shown to fulfil these criteria [2].

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Ascribing a specific pathogen as the cause of the encephalitis is not straightforward. The definitive or 'gold standard' way to establish an infectious aetiology is to identify the pathogen in diseased brain tissue. Whilst brain biopsy has 99% sensitivity and 100% specificity for herpes simplex encephalitis (HSE) its use is limited in the living as only a small amount of tissue is obtained for investigation, limited areas of the brain can be sampled, and the procedure may be associated with surgical complications [3]. Therefore a number of problems face both the diagnostician and researcher. First, in most cases it is not possible to study directly the diseased tissue. In addition, the frequency or strength of the link between the putative aetiological agent and the neurological syndrome varies among organisms.

Encephalitis is often described as a rare complication of common human infections. Thus, the detection of organisms outside the central nervous system (CNS) occurs with frequency, particularly for viruses that establish lifelong latency in their hosts such as lymphotropic and neurotropic herpesviruses. Other potentially neurotropic organisms are associated with asymptomatic carriage in non-sterile sites, such as the nasopharynx. Hence, detection of an organism in a non-sterile site or extraneural tissue confers less diagnostic weight than detection of an organism within brain tissue. Analysis of cerebrospinal fluid (CSF) is the key diagnostic intervention in patients with suspected CNS infections; however, being more representative of pathological processes affecting the meninges as opposed to the parenchyma of the brain it is only a surrogate for brain tissue. Furthermore, the methods of microbe detection have different diagnostic weight. For instance, isolation or culture of an organism indicates the presence of viable microbes, which cannot necessarily be implied when specific microbial sequences are detected by polymerase chain reaction (PCR). Therefore there exists a hierarchy of sample locations for attributing causality (see Fig. 1).

As Rivers classically demonstrated detection of a microbe is not sufficient to attribute causality but this association can be strengthened by demonstrating a microbe-specific immune response [2]. Serological tests may show primary or recent infection or activity, which confers more aetiological weight; particularly when the detected organism is one that establishes latency. Neurological complications are more frequent at the time of primary infection with viruses such as Epstein–Barr virus (EBV) or human herpesviruses-6 and -7 (HHV-6/-7) in the immunocompetent [4].

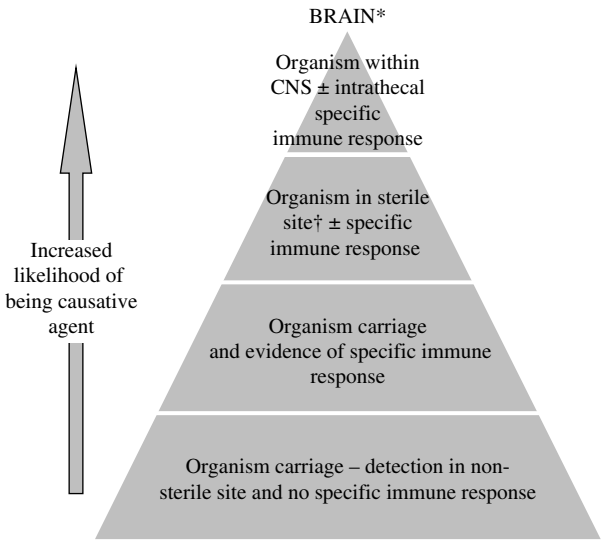

Fig. 1. Hierarchy of diagnostic tests for defining causal relationship between a microbe and the syndrome encephalitis. * This hierarchy is not relevant for all bacteria and viruses, e.g. rabies virus. † Normally sterile site = blood, CSF, joint, pleural, or pericardial fluid.

Furthermore, through study of CSF and blood samples paired in time, the microbe-specific immune response can be demonstrated to occur locally within the intrathecal space. When found this implies a very strong association between organism and neurological syndrome. Thus without brain biopsy the hierarchical zenith for diagnosis of infectious encephalitis would be both the demonstration of an organism and its specific immune response within the intrathecal space. Critically, however, infection is a dynamic process and therefore at different time points during infectious encephalitis the probability of detecting either the causal microbe or the microbe-specific immune response varies.

Approximately one third of acute encephalitides are thought to have an immune-mediated pathogenesis, with acute disseminated encephalomyelitis (ADEM), being the most commonly identified subtype [5]. The clinical manifestations of ADEM, often referred to as 'post-infectious' encephalitis, and acute infectious encephalitis may be identical and difficult to distinguish on clinical grounds alone [6]. There are at present no universally standardized diagnostic criteria for ADEM. Diagnosis is complicated and numerous controversies exist, for instance how to make the distinction from a first presentation of multiple sclerosis [7]. Other more recently described causes of immune-mediated encephalitis include voltage-gated potassium channel antibodies and

antibodies against the *N*-methyl-D-aspartate (NMDA) receptor [8–10].

This paper is the outcome of an initiative to streamline aetiological case definitions for acute encephalitis. Aetiological case definitions for encephalitis have recently emerged from the USA, but are otherwise lacking in the published literature [6, 11–13]. We present what is to our knowledge the first set of specific case definitions and laboratory criteria by organism for infectious causes of encephalitis and extend these to include immune-mediated causes. The more uniform case definitions are between regions, the more easily epidemiological studies of encephalitis can be compared.

METHODS

Discussions began on aetiological case definitions for acute encephalitis following implementation of the Health Protection Agency (HPA) Prospective Aetiological Study of Encephalitis in the UK (http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1195733813070?p=1191942149529) [14]. This study has involved national UK experts of encephalitis based both at the HPA and across the National Health Service. A diagnosis of encephalitis was made either clinically or pathologically (or both) as defined below. The aetiological case definitions apply to all cases with a clinical or histopathological diagnosis of encephalitis.

Encephalitis was defined as follows:

(1) *Clinical definition*: Any person, of any age, admitted to hospital with encephalopathy (altered level of consciousness persisting for >24 h and including lethargy, irritability or a change in personality and behaviour) and ⩾2 of the following:
- fever or history of fever (⩾38 °C);
- seizures and/or focal neurological findings (with evidences of brain parenchyma involvement);
- CSF pleocytosis (>4 WBC/μl);
- electroencephalogram findings compatible with encephalitis;
- abnormal results of neuroimaging in keeping with encephalitis.

(2) *Pathological definition*: The presence of non-pyogenic inflammatory infiltrates, commonly in the form of T lymphocytes and microglia, within the brain. This may also involve the meninges (meningoencephalitis) and spinal cord (myelitis). In polioencephalitis/poliomyelitis the inflammation is predominantly localized to grey matter, in leucoencephalitis to white matter, and in panencephalitis inflammation is present in both grey and white matter.

The causes were divided into those whose pathogenesis was due to a direct effect of the organism, and those with an immune-mediated pathogenesis. A combination of expert opinion and literature-based methods was used. The HPA Study Steering Group, all with extensive experience in encephalitis, provided multidisciplinary expertise in virology, microbiology, epidemiology, neurology, neuroimmunology, and infectious diseases. Individual advice on specific rarer causes of CNS infection, including amoebae, *Brucella*, *Borrelia*, *Leptospira* and *Toxoplasma* species, was obtained from UK reference laboratories whilst advice on antibody-associated encephalitis and histopathology was obtained from other laboratories with specific expertise. Guidance on diagnostic criteria for ADEM was sought from paediatric neurologists with expertise in this field. This expert opinion was supplemented by literature searches. Relevant articles on aetiology and diagnosis of encephalitis were retrieved from Pubmed by comprehensive albeit non-systematic searching. For 'aetiology' for example, specific criteria applicable to a particular agent were used to find relevant publications, e.g. 'granular cell neuronopathy' and 'fulminant JC encephalopathy' were entered to find papers specific to JC virus. The first meeting of the Steering Group to discuss these definitions was held in London in July 2007, with the first draft of the definitions circulated soon afterwards. Following a teleconference in November 2007 a subsequent draft was disseminated to the group. Specific questions and issues were addressed at a meeting held in January 2008 with an updated version circulated in November 2008, and a final review shortly after. Due to the complexities and caveats discussed above, we adopted a probabilistic approach for causal inference based on strength of association. Causes of encephalitis were defined as confirmed, probable, possible, and excluded (see Fig. 2). The category possible is not just used to capture diagnoses which are suggested but not confirmed by the available test results, but also to flag that a certain diagnosis has not been ruled out. The case definitions are primarily intended for use in clinical epidemiological studies of encephalitis. However, the definitions also have implications for clinicians, public health professionals and laboratory staff.

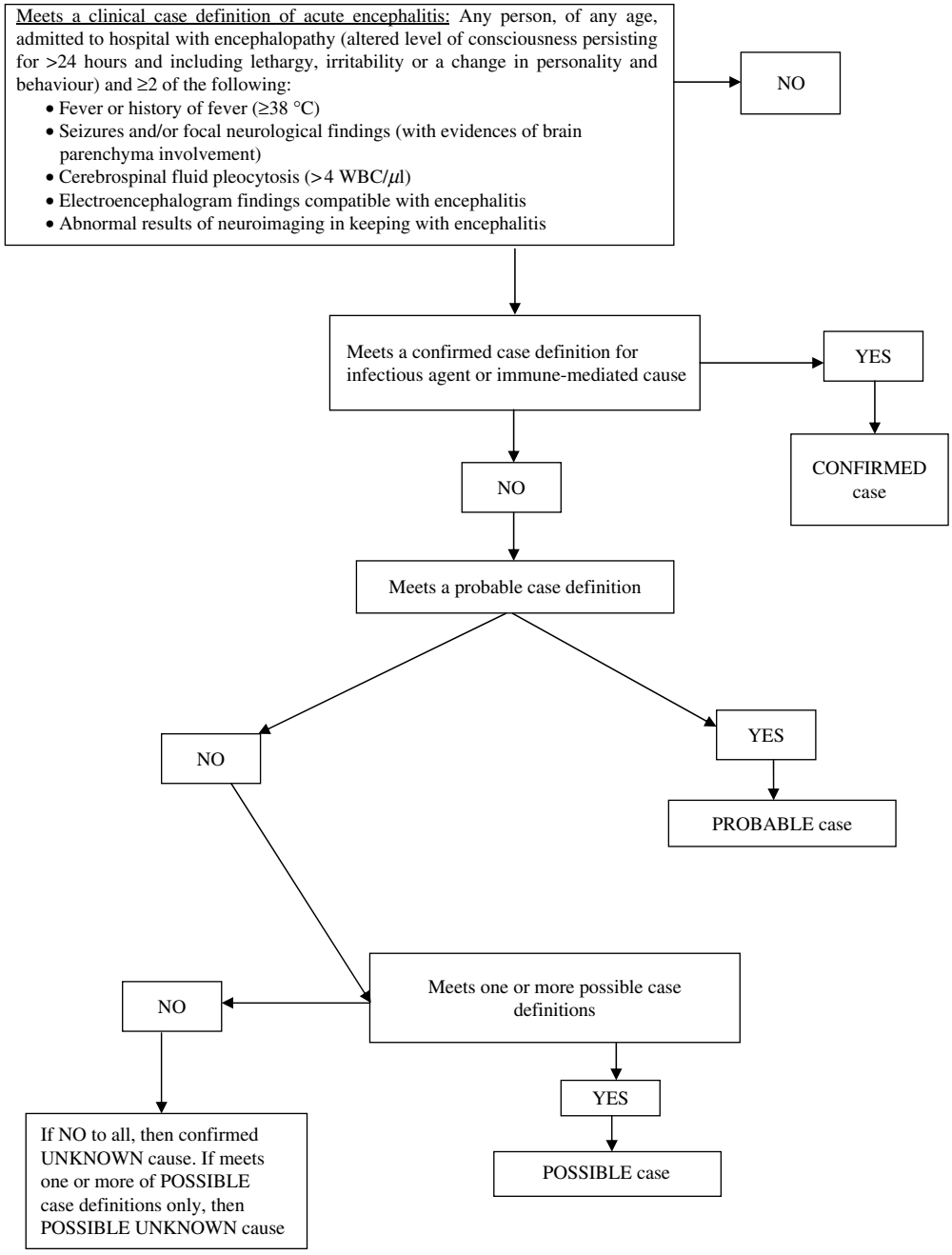

Fig. 2. Flowchart for defining aetiologies in acute encephalitis.

RESULTS

Aetiological case definitions for acute encephalitis caused by an acute infectious agent are displayed in Table 1. Case definitions for encephalitis which is predominantly immune-mediated are displayed in Table 2. These case definitions apply to all cases with a clinical picture of encephalitis or histopathological evidence of encephalitis (see Fig. 2).

DISCUSSION

Defining the causal relationship between a microbe and the syndrome encephalitis is complex. It is thought that over 100 different infectious agents may cause encephalitis, often as one of the rarer manifestations of infection. The gold-standard investigation to identify a causative agent in encephalitis is the examination of diseased brain tissue; however, in

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most cases this is not clinically justified. We present the UK perspective on aetiological case definitions for acute encephalitis. We also extend them to include immune-mediated causes, which often cannot be distinguished from acute infectious encephalitis on clinical grounds alone.

These case definitions are primarily the product of consultation with an array of experts with extensive experience in encephalitis; they have additionally been supplemented by a search of published literature. The complexities of defining aetiologies in encephalitis cannot be addressed from a single discipline but rather require a multidisciplinary effort like the one used for these purposes. Different approaches incorporate different perceptions and allow for establishment of a more precise set of definitions. Validation of these definitions in future studies of encephalitis will be beneficial, as will their application in paediatrics where the spectrum of causative agents and disease may be different.

Each organism should be considered separately as some are well-established causes of encephalitis whereas others have only recently been linked to the disease. Aetiological confirmation for the latter may require both nucleic acid detection in CSF and serological tests such as IgM and IgG antibody detection, whereas in the former only one of these may suffice. Nucleic acid detection by PCR may also be difficult to interpret as a positive result may be obtained in the absence of specific neurological signs, for example *Treponema* in syphilis. Other dimensions, including test type and sample type, need to be considered when defining the role of an agent in encephalitis. We emphasize the importance of detecting a specific intrathecal compartment effect or detection of the organism or nucleic acid within the CSF as this confers more aetiological weight. This is evident throughout our definitions and in many cases guides a confirmed *vs*. a probable categorization.

Inevitably difficulties were faced in producing these definitions. Differentiating between probable and possible cases is difficult, especially for viruses that establish latency within the host and are often common human infections that only occur sporadically as encephalitis. Negative post-mortem histology is not documented in the exclusion criteria for any cause. It is difficult to exclude diagnoses based on negative neuropathology unless the patient dies in the acute stage without treatment, and in some forms of encephalitis the low number of autopsy cases examined to date makes even this difficult without making assumptions. Documenting post-mortem criteria for organism confirmation is also difficult for some causes, for example HHV-6 and EBV, where histopathological evidence is based on data from only few cases. We propose a definition for the diagnosis of the syndrome ADEM although the cause or causes are still poorly defined. Perhaps in the future a similar set of definitions can be devised specifically for ADEM. Our case definitions have focused on the most common causes of encephalitis, as well as newly described antibody-mediated causes [8, 9]. Some immune-mediated forms of encephalitis are not included; however, those we do not discuss are of subacute onset and some are very contentious in terms of their existence, for example Hashimoto's encephalopathy/encephalitis.

Published studies have used different criteria to link potential aetiological agents to encephalitis. A recent French study used clinical data, imaging findings and biological test results to classify patients as having confirmed, probable or possible causes of encephalitis [15]. The California Encephalitis Project defined the association between an identified agent and the encephalitis case 'as *confirmed*, *probable* or *possible*, based on the type of specimen in which the potential aetiological organism was detected, the strength of the previously established associations between the agent and encephalitis, and the clinical and epidemiological characteristics of the disease' [13]. Parallels to our case definitions include the consideration of type of specimen, strength of previously established association, clinical characteristics, and emphasis on CNS to establish aetiology. In contrast, epidemiological profiles did not feature much in our case definitions. Only case definitions for certain agents, for example amoebae, *Borrelia burgdorferi* and rabies, included epidemiological criteria; exposures are very well defined for these organisms. Although our main emphasis was laboratory criteria, we integrate imaging and histopathology into our case definitions. For example, 'MRI suggestive/not suggestive of ADEM' is used to differentiate acute infectious and post-infectious encephalitis associated with group A streptococci and *M. pneumoniae*, as the pathogenic mechanisms for these organisms remain unclear. A characteristic MRI was also used to define HIV and JC cases as sufficient evidence is available on which to base these diagnostic criteria [16, 17]. Recent US clinical practice guidelines for the management of encephalitis emphasize the importance of neuroimaging in encephalitis and imply its potential use in

Table 1. *Acute encephalitis caused by an infectious agent*

	Confirmed	Probable	Possible*	Excluded
AMOEBAE				
Naegleria fowleri [22]	• Clinical presentation consistent with PAM, and history of recent swimming or other immersion in fresh water; AND • Demonstration of motile amoebae on wet mount preparations of fresh CSF, or on Giemsa/Wright stained smears of CSF; OR • Positive culture from CSF or brain tissue; OR • Autopsy neuropathology demonstrates haemorrhagic meningo-encephalitis with amoebic trophozoites, but absence of cysts	• Clinical presentation consistent with PAM, and history of recent swimming or other immersion in fresh water; AND • Autopsy neuropathology demonstrates haemorrhagic meningo-encephalitis; AND • No other explanatory pathogen or cause found		• No amoebae detectable in CSF or brain pathology; OR • Meets confirmed or probable CD for another cause
Acanthamoeba spp., *Balamuthia mandrillaris* [22]	• Clinical presentation consistent – insidious chronic onset, with or without a history of soil exposure; AND • Demonstration of motile amoebae on wet mount preparations of fresh CSF, or on Giemsa/Wright stained smears of CSF (rare); OR • Cysts and trophozoites in brain tissue; OR • Culture positive (rare); OR • Autopsy neuropathology demonstrates necrotic and haemorrhagic meningo-encephalitis with scattered amoebic trophozoites and cysts, and giant multinucleate cells/granuloma	• Clinical presentation consistent – insidious chronic onset, with or without a history of soil exposure; AND • Autopsy neuropathology demonstrates necrotic and haemorrhagic meningo-encephalitis; AND • No other explanatory pathogen or cause found		
BACTERIA				
Bartonella henselae	• *Bartonella* detected in CSF/brain specimens by PCR (rare); OR • *Bartonella*-specific intrathecal antibody response†; AND • *If available* – Autopsy neuropathology demonstrates perivascular inflammation and microglial nodules‡; AND • No other explanatory pathogen or cause found	• ⩾4-fold rise in blood antibody titres; OR • Positive PCR of lymph node tissue; AND • No other explanatory pathogen or cause found	• Single elevated antibody titre	• *Bartonella* not detected in CSF/brain specimens by PCR; AND • No serolgical evidence in serum; OR • Meets confirmed or probable CD for another cause
Borrelia burgdorferi (Lyme borreliosis) [23–26]	• Preceding risk of tick exposure; AND • *B. burgdorferi*-specific intrathecal antibody response†; OR • Isolation of *B. burgdorferi* from CSF or CNS sample (rare and likely only to occur in early neuroborreliosis) or detection of *B. burgdorferi* DNA by PCR in CSF or CNS tissue	• Preceding risk of tick exposure; AND • Seroconversion or significant rise in antibody level on serum samples obtained 2 weeks apart and tested in parallel in patients with suspected early neuroborreliosis	• Preceding risk of tick exposure; AND • Clinical history (e.g. erythema migrans) compatible with earlier stage of infection; OR • *B. burgdorferi* antibodies present in serum	• Absence of preceding tick exposure risk; OR • *B. burgdorferi* serology not present in serum 4 weeks after presentation in an immunocompetent patient; OR • Absence of intrathecal *B. burgdorferi* antibody synthesis 2 weeks after onset; OR • Meets confirmed or probable CD for another cause and does not meet the possible CD for *B. burgdorferi*

Brucella spp. [27]	• Epidemiological criteria: contact with infected animals; OR consumption of unpasteurized milk/milk products from enzootic country; OR residence in or travel to enzootic country; AND • *Brucella*-specific intrathecal antibody response†; OR • ⩾4-fold rise in *Brucella* agglutination titre AND other *Brucella* antibody tests between acute- and convalescent-phase serum specimens obtained ⩾2 weeks apart and studied at the same laboratory	• Epidemiological criteria: contact with infected animals; OR consumption of unpasteurized milk/milk products from enzootic country; OR residence in or travel to enzootic country; AND • Supportive serology (i.e. *Brucella* agglutination titre of ⩾160 in one or more serum specimens obtained after onset of symptoms, with diagnostic titres in other *Brucella* antibody tests)		• *Brucella* serology negative in an immunocompetent patient; OR • Meets confirmed or probable CD for another cause
Chlamydophila spp.	• *Chlamydophila* spp. detected in CSF/brain specimens by PCR; OR • *Chlamydophila*-specific intrathecal antibody response†; AND • No other explanatory pathogen or cause found		• Four-fold rise in antibody titre, culture-based or PCR evidence of infection outside the CNS site	• Meets confirmed or probable CD for another cause and does not meet the possible CD for *Chlamydophila*
Group A streptococci (*Streptococcus pyogenes*)	• Detection of group A streptococcal nucleic acid in CSF/brain specimens by PCR or culture§; AND • No MRI changes suggestive of ADEM	• Increased antistreptolysin-O or other streptococcal antibodies; AND • No MRI suggestive of ADEM; AND • No other explanatory pathogen or cause found	• Throat culture positive for group A streptococcus (in the context of sore throat); OR • Recent scarlet fever	• ASOT negative at 4 weeks after presentation in an immunocompetent patient; OR • Meets confirmed or probable CD for another cause and does not meet the CD for group A streptococci
Haemophilus influenzae¶	• Detection of *H. influenzae* or *H. influenzae* nucleic acid from a normally sterile site (e.g. blood, CSF or, less commonly, joint, pleural, or pericardial fluid)	• Detection of *H. influenzae* antigen from a normally sterile site; AND • No other explanatory pathogen or cause found	• Case with clinical epiglottitis without any laboratory confirmation or with identification only from non-sterile site (consider vaccine history)	• *H. influenzae* not detected in any sterile site; OR • Meets confirmed or probable CD for another cause and does not meet the possible CD for *H. influenzae*
Leptospira spp.	• Isolation of leptospires from blood or CSF; OR • ⩾4-fold increase in *Leptospira* agglutination titre between acute- and convalescent-phase serum specimens obtained ⩾2 weeks apart and studied at the same laboratory; OR • Demonstration of leptospires in fixed or unfixed tissue by immunofluorescence	• Serological evidence of acute infection (IgM positive or single high titre of ⩾200); AND • No other explanatory pathogen or cause found; AND • Suggestive epidemiological features	• Negative serology but compatible clinical features and exposure within 19 days of onset	• *Leptospira* serology negative at 4 weeks after presentation in an immunocompetent patient; AND • No suggestive epidemiological features; OR • Meets confirmed or probable CD for another cause
Listeria monocytogenes	• Isolation/PCR of *L. monocytogenes* from a normally sterile site; OR • In the setting of miscarriage or stillbirth, isolation of *L. monocytogenes* from placental or foetal tissue		Strong epidemiological evidence e.g. consumption of contaminated food in an outbreak, and a brainstem encephalitis (with negative PCR and CSF culture)	• Meets confirmed or probable CD for another cause and does not meet the possible CD for *L. monocytogenes*
Mycobacterium tuberculosis	• MTB culture/PCR positive in CSF; OR • Autopsy neuropathology demonstrates basal meningitis with granuloma and AAFBs	• MTB culture/PCR positive outside CNS site; OR • Decision to treat (based on epidemiology, CSF chemistry, and clinical signs); AND • AAFBs inside/outside CNS site; OR • Histological appearance of granulomata; OR • Decision to treat; AND • Response to treatment; AND • No other explanatory pathogen or cause found	• Decision to treat	• No decision to treat; AND • Negative microbiological investigations; OR • Meets confirmed or probable CD for another cause and does not meet the possible CD for MTB

Table 1 (*cont.*)

	Confirmed	Probable	Possible*	Excluded
Mycoplasma pneumoniae	• *M. pneumoniae* detected in CSF/brain specimens by PCR; OR • *M. pneumoniae* -specific intrathecal antibody response†; AND • No MRI suggestive of ADEM; AND • No other explanatory pathogen or cause found	• Serological evidence of acute infection (⩾4-fold rise in CFT or agglutination titres or positive IgM response); AND • No MRI suggestive of ADEM; AND • No other explanatory pathogen or cause found	• Serological (single raised titre), culture-based or PCR evidence of infection outside the CNS site	• Meets confirmed or probable CD for another cause and does not meet the possible CD for *M. pneumoniae*
Neisseria meningitidis¶	• Detection of *N. meningitidis, N. meningitidis* nucleic acid or *N. meningitidis* antigen or isolation of *N. meningitidis* from a normally sterile site (e.g. blood, CSF or, less commonly, joint, pleural, or pericardial fluid)	• Detection of *N. meningitidis* from a non-sterile site; OR • Clinical picture compatible with meningococcal disease (e.g. meningitis and/or meningococcemia that may progress rapidly to purpura fulminans, shock and death. Other manifestations are possible) without any laboratory confirmation; OR • Demonstration of Gram-negative diplococci from normally sterile site by microscopy; AND • No other explanatory pathogen or cause found	• Meets confirmed or probable CD; AND • Group A, C, Y or W135 detected, AND patient ⩾12 months and been vaccinated for the matching serogroup at ⩾12 months, OR was <12 months of age and had received at least 2 doses of vaccine more than 1 month prior to onset	• *N. meningitidis* not detected in any sterile site; OR • Meets confirmed or probable CD for another cause
Other acute bacterial ME (e.g. group B streptococci)	• Detection of bacterial nucleic acid in CSF/brain specimens by PCR or culture			
Streptococcus pneumoniae¶	• Detection of *S. pneumoniae* from a normally sterile site by culture; OR • Detection of *S. pneumoniae* DNA from CSF or blood (except for blood in children <2 years of age) by dual target PCR; OR • Reference laboratory identification of *S. pneumoniae* C polysaccharide and serotype-specific antigen in CSF	• Identification of *S. pneumoniae* C polysaccharide and serotype-specific antigen in urine (except for urine in children <2 years of age)	• Clinical diagnosis where the responsible clinician or microbiologist considers that pneumococcal disease, based on available clinical, microbiological and epidemiological evidence, is the most likely diagnosis. A probable case would be supported by certain clinical signs or an epidemiological link to a confirmed case; OR • Meets confirmed or probable CD; AND • Vaccine-preventable serogroup detected (this needs to be checked as serogroups included by vaccine vary) AND patient ⩾12 months and had been vaccinated against matching serogroup at ⩾12 months OR was <12 months of age and had received at least 2 doses of vaccine more than 1 month prior to onset	• *S. pneumoniae* not detected in any sterile site; OR • Meets confirmed or probable CD for another cause and does not meet the possible CD for *S. pneumoniae*

Treponema pallidum	• Syphilis of any clinical stage; AND • Reactive serological test for syphilis and reactive VDRL/RPR and/or TPHA/TPPA in CSF; OR • *T. pallidum* detected by PCR in CSF; OR • Autopsy neuropathology demonstrates a chronic meningo-encephalitis with demonstration of treponemes by silver impregnation	• Syphilis of any clinical stage; AND • Negative VDRL/RPR and TPHA/TPPA in CSF; AND • Elevated CSF protein or leukocyte count in the absence of other known causes of these abnormalities; AND • Clinical symptoms or signs consistent with neurosyphilis without other known causes for these clinical abnormalities	• Syphilis serology negative at 4 weeks after presentation in an immunocompetent patient; OR • Meets confirmed or probable CD for another cause
PARASITES			
Toxoplasma gondii [28]	• *T. gondii* detected in any CSF/brain specimens by PCR; OR • *Toxoplasma*-specific intrathecal antibody response†; OR • Autopsy neuropathology demonstrates a panencephalitis with *T. gondii* antigen in zoites	• *T. gondii* not detected in CSF/brain specimens but there is strong serological evidence of infection (IgM or dye test)	• *Toxoplasma* serology negative at 4 weeks after presentation in an immunocompetent patient; OR • Meets confirmed or probable CD for another cause
RICKETTSIA			
Coxiella burnetii	• ⩾4-fold change in antibody titre to *Coxiella* phase II or phase I antigen in paired serum specimens ideally taken 3–6 weeks apart; OR • Demonstration of *Coxiella* in a clinical specimen by detection of antigen or nucleic acid	• Single high titre (to be discussed with reference laboratory on an individual case basis)	• *Coxiella* serology negative at 4 weeks after presentation in an immunocompetent patient; OR • Meets confirmed or probable CD for another cause
Ehrlichia spp.	• ⩾4-fold increase in antibody titre to *Ehrlichia* antigen by IFA, in acute and convalescent-phase specimens ideally taken ⩾4 weeks apart. HME diagnosis requires *E. chaffeensis* antigen, and HGE currently requires *E. equi* or HGE-agent antigen; OR • Intracytoplasmic morulae identified in blood, bone marrow, or CSF leukocytes AND an IFA antibody titre ⩾64	• Single high titre (to be discussed with reference laboratory on an individual case basis)	• *Ehrlichia* serology negative at 4 weeks after presentation in an immunocompetent patient; OR • Meets confirmed or probable CD for another cause
Rickettsia spp.	• ⩾4-fold rise in antibody titre to rickettsial antigen by IFA, CF, LA, MA, or IHA test, or a single titre ⩾64 by IFA or ⩾16 by CF; OR • Demonstration of positive immuno-fluorescence of skin lesion (biopsy) or organ tissue (autopsy); OR • Isolation of *Rickettsia* from a clinical specimen; OR • Autopsy neuropathology demonstrates a microvasculitis with rickettsial antigen in endothelial cells	• Single high titre (to be discussed with reference laboratory on an individual case basis)	• *Rickettsia* serology negative at 4 weeks after presentation in an immunocompetent patient; OR • Meets confirmed or probable CD for another cause

Table 1 (*cont.*)

	Confirmed	Probable	Possible*	Excluded
VIRUSES				
Adenovirus	• ADV detected in CSF/brain specimens by PCR; OR • ADV-specific intrathecal antibody response†; OR • Autopsy neuropathology demonstrates basophilic nuclear inclusions in neurons and glia containing ADV DNA/antigen, variable inflammation, necrosis and haemorrhage‡; AND • No other explanatory pathogen or cause found		• Serological evidence of primary ADV infection; OR • ADV DNA/antigen detected in a blood, respiratory, urine or faecal sample (excluding adenovirus 40 & 41 in faecal samples)	• ADV DNA negative on CSF specimen taken 3–7 days after symptom onset; AND • No ADV-specific intrathecal antibody response† at least 7–10 days after symptom onset; OR • Meets confirmed or probable CD for another cause and does not meet the possible CD for ADV
Cytomegalovirus	• CMV DNA/antigen detected in any CSF/brain specimens; OR • CMV-specific intrathecal antibody response†; OR • Autopsy neuropathology demonstrates panencephalitis with microglial nodules and cytomegalic inclusions containing CMV DNA/antigen; AND • No other explanatory pathogen or cause found		• Serological evidence of primary CMV infection (e.g. seroconversion); OR • CMV DNA/antigen detected in blood	• CMV DNA negative on CSF specimen taken 3–7 days after symptom onset; AND • No CMV-specific intrathecal antibody response† at least 7–10 days after symptom onset; OR • Meets confirmed or probable CD for another cause and does not meet the possible CD for CMV
Enteroviruses	• Enteroviruses detected in any CSF/brain specimens; OR • Enterovirus-specific intrathecal antibody response†; AND • *If available* – Autopsy neuropathology demonstrates poliomyelitis/polioencephalitis AND • No other explanatory pathogen or cause found		• Laboratory detection of organism outside the CNS; OR • Serological evidence of recent infection	• Meets confirmed or probable CD for another cause and does not meet the possible CD for enterovirus
Epstein–Barr virus	• EBV DNA/antigen detected in any CSF/brain specimens; AND • Serological evidence of primary EBV infection (includes positive heterophile antibody test and/or EBV VCA IgM positive plus anti-EBNA IgG negative); AND • No other explanatory pathogen or cause found; OR • Autopsy neuropathology demonstrates EBV DNA/RNA/antigen detected in brain tissue, variable, mild inflammation, may involve nerve roots and spinal cord (exclude patients with primary CNS lymphoma)‡	• EBV DNA/antigen detected in any CSF/brain specimens; AND • No other explanatory pathogen or cause found and primary CNS lymphoma excluded in the immunosuppressed	• Serological evidence of primary EBV infection	• EBV DNA negative on CSF specimen taken 3–7 days after symptom onset; AND • No EBV-specific intrathecal antibody response† at least 7–10 days after symptom onset; OR • Meets confirmed or probable CD for another cause and does not meet the possible CD for EBV

Herpes simplex virus [29, 30]	• HSV DNA/antigen detected in any CSF/brain specimens; OR • HSV-specific intrathecal antibody response†; OR • Autopsy neuropathology demonstrates panencephalitis with HSV DNA/antigen present in eosinophilic neuronal inclusions	(1) In ALL: • Evidence of primary HSV infection (IgG seroconversion or detection of low avidity antibodies) within 2 weeks of onset (2) In infants ⩽1 year: • IgM positive in blood; AND • PCR swab positive from any site	• Serological evidence suggestive but not conclusive (IgM positive) of primary HSV infection or positive sample other than CNS site	• HSV DNA negative on CSF specimen taken 3–7 days after symptom onset; AND • No HSV-specific intrathecal antibody response† at least 7–10 days after symptom onset; OR • Meets confirmed or probable CD for another cause and does not meet the possible CD for HSV
Human herpesvirus-6 [18]	(1) In immunocompromised: • Clinical picture of encephalitis in allogeneic haematopoietic stem cell and solid organ transplant patients [31]; AND • HHV-6 detected in CSF/brain; AND • Exclusion of HHV-6 chromosomal integration (*This is defined by characteristically high, persistent HHV-6 DNA levels in whole blood equivalent to at least 1 copy/leukocyte and in serum or plasma equivalent to at least 1 copy/lysed leukocyte*); OR • Autopsy neuropathology demonstrates HHV-6 DNA/antigen in neurons and glia, panencephalitis‡ (2) In immunocompetent: • Primary HHV-6 infection; AND • HHV-6 detected in CSF/ brain; AND • Exclusion of HHV-6 chromosomal integration	(1) In immunocompromised: • Clinical picture of encephalitis in allogeneic stem cell and solid organ transplant patients; AND • HHV-6 detected in CSF/brain; OR • Autopsy neuropathology? demonstrates HHV-6 DNA/antigen in neurons and glia, panencephalitis (2) In immunocompetent: • Primary HHV-6 infection; AND • HHV-6 detected in CSF or brain	• No evidence of primary HHV-6 infection; AND • HHV-6 detected in CSF/brain; AND • HHV-6 chromosomal integration should be excluded	• Meets confirmed or probable CD for another cause and does not meet the possible CD for HHV-6
Human herpesvirus-7	• Primary HHV-7 infection; AND • HHV-7 detected in CSF/brain		• No evidence of primary HHV-7 infection; AND • HHV-7 detected in CSF/brain	• Meets confirmed or probable CD for another cause and does not meet the possible CD for HHV-7
Human immunodeficiency virus	• HIV RNA detected in any CSF/brain specimens by PCR; AND • MRI findings consistent with HIV; AND • No other cause identified; OR • Autopsy neuropathology demonstrates panencephalitis or leukoencephalitis with HIV antigen in macrophages	• HIV RNA present in the CSF at a higher viral load than plasma in samples taken at approximately the same time; AND • No other explanatory pathogen or cause found	• Clinical illness in the context of HIV seroconversion where no CSF viral load was done but there is evidence of a pleocytosis	• Meets confirmed or probable CD for another cause and does not meet the possible CD for HIV

Table 1 (*cont.*)

	Confirmed	Probable	Possible*	Excluded
Influenza A/B	• Influenza virus RNA detected in CSF/brain specimens by PCR; OR • Influenza-specific intrathecal antibody response†; AND • No other explanatory pathogen or cause found (*If well-matched vaccine given >2 weeks before or the 2-dose schedule completed for children, move to probable*)	• Serological evidence of acute influenza infection (⩾4-fold rise in antibody titres in paired serum); AND • No other explanatory pathogen or cause found (*If well-matched vaccine given >2 weeks before or the 2-dose schedule completed for children, move to possible*)	• Single high antibody titre to influenza in a blood specimen; OR • Influenza virus RNA/antigen detected in a respiratory, urine or faecal sample	• Influenza virus RNA negative on CSF specimen taken 3–7 days after symptom onset; AND • No influenza-specific intrathecal antibody response† at least 7–10 days after symptom onset; OR • Meets confirmed or probable CD for another cause and does not meet the possible CD for influenza
Japanese encephalitis virus [32]	• Presence of JEV-specific IgM antibody in single sample of CSF, as detected by IgM-capture ELISA specifically for JEV. This should be confirmed by specific neutralising titres to distinguish from cross-reactive flaviviruses such as WNV, SLEV, dengue and possibly TBE (depending on patient's exposures); OR • Detection of JEV antigens in tissue by immunohistochemistry; OR • Isolation of JEV from or detection of JEV genome in CSF or tissue by reverse transcriptase PCR or an equally sensitive and specific nucleic acid amplification test; OR • Autopsy neuropathology demonstrates panencephalitis with JEV antigen in neurons	• Presence of JEV-specific IgM antibody in single sample of serum, as detected by IgM-capture ELISA; OR • Detection of JEV genome in serum, plasma, or blood by reverse transcriptase PCR or an equally sensitive and specific nucleic acid amplification test; OR • Isolation of JEV from serum, plasma or blood; OR • Detection of ⩾4-fold rise in JEV-specific antibody as measured by haemagglutination inhibition or plaque reduction neutralization assay in serum collected during acute and convalescent phase of illness. The two specimens for IgG should be collected at least 14 days apart. The IgG test should be performed in parallel with other confirmatory tests to eliminate possibility of cross-reactivity	• Presence of IgG antibodies to JEV	• No JEV detected in CSF; OR • No intrathecal or serological antibodies to JE detected; OR • Meets confirmed or probable CD for another cause and does not meet the possible CD for JEV
JC polyomavirus	• JC virus detected in any CSF/brain specimens by PCR; OR • JC-specific intrathecal antibody response†; AND • Compatible illness/MR scan findings consistent with PML, granular cell neuronopathy, or fulminant JC encephalopathy [33, 34]; OR • Autopsy neuropathology demonstrates leucoencephalitis with demyelination and JC DNA/antigen in glia	• Compatible illness/MR scan findings consistent with PML		• Meets confirmed or probable case definition for another cause
Lymphocytic choriomeningitis virus	• LCMV detected in any CSF/brain specimens; OR • LCMV-specific intrathecal antibody response†	• Serological evidence of acute infection (IgM positive); AND • No other explanatory pathogen or cause found		• Meets confirmed or probable CD for another cause

Measles	• Measles virus/nucleic acid detected in any CSF/brain specimens; OR • Measles-specific intrathecal antibody response†; OR • Autopsy neuropathology demonstrates panencephalitis with intranuclear inclusions containing measles virus RNA/antigen		• IgG seroconversion or detection of IgM in serum, plasma or oral fluid, or detection of measles virus/nucleic acid by PCR on oral fluid or urine. Samples should be within 2 weeks after symptom onset. OR • Meets confirmed or probable CD; AND • Measles vaccine given at least 1 month apart and the second at least 1 month before onset	• Evidence of prior immunity at presentation (IgG, no IgM, or $\geqslant$2 doses of vaccine); OR • Meets confirmed or probable CD for another cause and does not meet the possible CD for measles
Mumps	• Mumps virus/nucleic acid detected in any CSF/brain specimens; OR • Mumps-specific intrathecal antibody response†		• IgG seroconversion or detection of IgM in serum, plasma or oral fluid, or detection of mumps virus/nucleic acid by PCR on oral fluid or urine. Samples should be within 2 weeks after symptom onset; OR • Meets confirmed or probable CD; AND • Mumps vaccine given at least 1 month apart and the second at least 1 month before onset	• Evidence of prior immunity at presentation (IgG, no IgM, or $\geqslant$2 doses of vaccine); OR • Meets confirmed or probable CD for another cause and does not meet the possible CD for mumps
Norovirus	• Norovirus detected in CSF/brain specimens by PCR; OR • Norovirus-specific intrathecal antibody response†; AND • No other explanatory pathogen or cause found		• Detection of norovirus outside CNS	• Meets confirmed or probable CD for another cause and does not meet the possible CD for norovirus
Other arboviruses – including California serogroup viruses, Eastern equine, Venezuelan equine, Murray Valley, Rocio virus, Rift Valley fever, St Louis, Western equine, Powassan, Toscana, Chikungunya, and Usutu viruses [35]	• Isolation of virus from or demonstration of specific viral antigen or genomic sequences in brain tissue/CSF; OR • Virus-specific IgM antibodies demonstrated in CSF by antibody-capture EIA; OR • Autopsy neuropathology demonstrates a panencephalitis with demonstration of viral RNA/antigen in glia	• Isolation of virus from or demonstration of specific viral antigen or genomic sequences in other tissue, blood, or other body fluid or body tissue other than brain; OR • $\geqslant$4-fold change in virus-specific serum antibody titre; OR • Virus-specific IgM antibodies demonstrated in serum by antibody-capture EIA and confirmed by demonstration of virus-specific serum IgG antibodies in the same or a later specimen by another serologic assay (e.g. neutralization or HI)	• A single or stable ($\leqslant$2-fold change) but elevated titre of virus-specific serum antibodies OR serum IgM antibodies detected by antibody-capture EIA but with no available results of a confirmatory test for virus-specific serum IgG antibodies in the same or a later specimen	• No virus detected in CSF or brain; OR • No virus antibody detected in CSF or serum; OR • Meets confirmed or probable CD for another cause

Table 1 (*cont.*)

	Confirmed	Probable	Possible*	Excluded
Rabies	• Detection by direct fluorescent antibody of rabies antigens in a clinical specimen (preferably brain or nerves surrounding hair follicles in the nape of the neck); OR • Isolation (in cell culture or in a laboratory animal) of rabies virus or positive rabies PCR from saliva, CSF, or CNS tissue; OR • Identification of a rabies-neutralizing antibody titre $\geqslant 5$ in the serum or CSF of an unvaccinated person; OR • Autopsy neuropathology demonstrates a polioencephalitis with eosinophilic neuronal cytoplasmic inclusions (Negri bodies)	• Clinical presentation and outcome consistent with rabies; AND • History of exposure to a rabid animal within the incubation period	• Clinical presentation consistent with rabies; AND • No history of exposure to a rabid animal within the incubation period	• The patient survives (applies only if patient unvaccinated or had not received post-exposure prophylaxis); OR • Meets confirmed or probable CD for another cause and does not meet the possible CD for rabies
Respiratory syncytial virus	• RSV detected in CSF/brain specimens by PCR; OR • RSV-specific intrathecal antibody response†; AND • No other explanatory pathogen or cause found		• Serological evidence of primary RSV infection; OR • RSV RNA/antigen detected in a blood, respiratory, urine or faecal sample	• RSV RNA negative on CSF specimen taken 3–7 days after symptom onset; AND • No RSV-specific intrathecal antibody response† at least 7–10 days after symptom onset; OR • Meets confirmed or probable CD for another cause and does not meet the possible CD for RSV
Rotavirus	• Rotavirus detected in CSF/brain specimens by PCR; OR • Rotavirus-specific intrathecal antibody response†; AND • No other explanatory pathogen or cause found		• Detection of rotavirus outside CNS; AND • No other explanatory pathogen or cause found	• Meets confirmed or probable CD for another cause and does not meet the possible CD for rotavirus
Rubella	• Rubella virus detected in any CSF/brain specimens; OR • Rubella-specific intrathecal antibody response†; AND • *If available* – Autopsy neuropathology demonstrates a panencephalitis AND • No other explanatory pathogen or cause found		• IgG seroconversion or detection of IgM in serum, plasma or oral fluid, or detection of rubella virus/nucleic acid by PCR on oral fluid or urine. Samples should be within 2 weeks after symptom onset; OR • Meets confirmed or probable CD; AND • Rubella vaccine given at least 1 month before onset	• Evidence of prior immunity at presentation (IgG, no IgM, or $\geqslant 2$ doses of vaccine); OR • Meets confirmed or probable CD for another cause and does not meet the possible CD for rubella

Tick-borne encephalitis virus	• Detection of TBEV-specific IgM or IgG antibodies in CSF; OR • Virus isolation from tissue or CSF; OR • Autopsy neuropathology demonstrates a polioencephalitis with TBEV viral antigen in neurons and glia	• ⩾4-fold rise in serum antibody titre, with no history of vaccination against any flaviviral disease during previous 3 months; OR • Detection of specific IgM antibodies in serum, with no history of vaccination against any flaviviral disease during previous 3 months; preferably with confirmation by neutralisation; OR • Viral isolation from blood		• Serology negative 10–14 days after symptom onset; OR • Meets confirmed or probable CD for another cause
Varicella-zoster virus	• VZV DNA/antigen detected in any CSF/brain specimens; OR • VZV-specific intrathecal antibody response†; OR • Autopsy neuropathology demonstrates panencephalitis with nuclear inclusions containing VZV DNA/antigen	• Serological evidence of VZV primary infection (IgG seroconversion or detection of low avidity antibodies) within 2 weeks of onset	• Serological evidence suggestive but not conclusive (IgM positive) of primary VZV infection or virus detection at a site other than the CNS	• VZV DNA negative on CSF specimen taken 3–7 days after symptom onset; AND • No VZV-specific intrathecal antibody response† at least 7–10 days after symptom onset; OR • Meets confirmed or probable CD for another cause and does not meet the possible CD for VZV
West Nile virus	• Detection of antibody in CSF via MAC-ELISA and differentiation from other flaviviruses by plaque reduction neutralization test; OR • Detection of WNV in CSF by PCR; OR • Autopsy neuropathology demonstrates polioencephalitis with WNV antigen in neurons	• Detection of IgM antibody in serum via MAC-ELISA and differentiation from other flaviviruses; preferably with confirmation by neutralisation; OR • Detection of WNV in serum by PCR	• Exposure during WNV epidemic but inappropriate or untimely sampling	• No WNV detected in CSF or brain; OR • No WNV antibody detected in CSF or serum; OR • Meets confirmed or probable CD for another cause

ADEM, Acute disseminated encephalomyelitis; ADV, adenovirus; AAFB, alcohol and acid-fast bacilli; ASOT, antistreptolysin O titre; CD, case definition; CF, complement fixation; CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; EBNA, Epstein–Barr virus nuclear antigen; EBV, Epstein–Barr virus; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; HGE, human granulocytic ehrlichiosis; HHV-6, human herpesvirus-6; HHV-7, human herpesvirus-7; HI, haemagglutination inhibition; HIV, human immunodeficiency virus; HME, human monocytic ehrlichiosis; HSV, herpes simplex virus; IFA, immunofluorescence assay; IHA, indirect haemagglutination; JEV, Japanese encephalitis virus; LA, latex agglutination; LCMV, lymphocytic choriomeningitis virus; MA, microagglutination; MAC-ELISA, IgM antibody capture ELISA; ME, meningoencephalitis; MRI, magnetic resonance imaging; MTB, *Mycobacterium tuberculosis*; PAM, primary amoebic meningoencephalitis; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy; RPR, rapid plasma reagin; RSV, respiratory syncytial virus; SLEV, St Louis encephalitis virus; TBEV, tick-borne encephalitis virus; TPHA, treponema pallidum haemagglutination test; TPPA, treponema pallidum particle agglutination test; VCA, viral capsid antigen; VDRL, venereal disease research laboratory; VZV, varicella-zoster virus; WNV, West Nile virus.

* Patients may meet more than one possible aetiological case definition but only one probable aetiological case definition.

† Intrathecal antibody production implies local synthesis of microbe-specific antibody within the CNS. Microbe-specific intrathecal antibody production can be identified by two methodologies: either by calculation of an antibody index or through antigen-specific immunoblotting of CSF and serum antibody following isoelectric focusing [36].

‡ Based on data from very few cases.

§ Does not include post-infectious encephalitis due to streptococci.

¶ Presents more often as meningoencephalitis.

Table 2. *Encephalitis which is predominantly immune-mediated*

	Confirmed	Possible*	Excluded
ADEM [5, 6, 37–43]	**Defining case** • A direct infectious aetiology is excluded; AND • Prior to the onset of the current illness, the patient has not suffered previous neurological symptoms suggestive of demyelination; AND • The MRI findings are compatible with ADEM (see below) or diagnosis confirmed by biopsy or post-mortem examination; AND • The patient does not develop definite MS during the duration of the study; OR • Post-mortem/autopsy findings are in keeping with ADEM (Note: instead of or as well as MRI criteria) **Schwartz MRI criteria** • One or multiple supra- or infratentorial demyelinating lesions; AND • Absence of 'black holes' on T1-weighted imaging (indicative of previous destructive inflammatory-demyelinating illness) **Defining aetiology** • There is serological evidence of contemporary microbial infection; OR • A microbe is directly identified outside the CNS with evidence of infection	• Encephalitic illness in the setting of systemic illness with known association with ADEM, e.g. measles; OR • Encephalitis following vaccination (particularly with inactivated agent)	• Post-mortem CNS examination excluding the diagnosis in untreated patient who dies during acute illness
Bickerstaff's encephalitis [44]	• The patient has progressive, symmetric external ophthalmoplegia and ataxia within 4 weeks of disease onset with disturbance of level of consciousness or hyper-reflexia; AND • The following brainstem conditions excluded – vascular disease, Wernicke's, botulism, myasthenia gravis, brainstem tumour, pituitary apoplexy, ADEM, MS, neuro-Behcet's, vasculitis and lymphoma		
Voltage-gated potassium channel antibodies [9]	• A titre of >400 pM; AND • No other explanatory pathogen or cause found	• A titre of 100–400 pM	
Anti-NMDA receptor antibodies [8]	• Detection of anti-NMDA receptor antibodies; AND • Immunotherapy-responsive; AND • No other explanatory pathogen or cause found		
Anti-GAD antibodies	• Detection of anti-GAD65 antibodies (>20 nmol/l); AND • Immunotherapy-responsive; AND • No other explanatory pathogen or cause found		

ADEM, Acute disseminated encephalomyelitis; CNS, central nervous system; GAD, glutamic acid decarboxylase; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMDA, *N*-methyl-D-aspartate.

* Patients may meet more than one possible aetiological case definition but only one probable aetiological case definition.

distinguishing aetiologies [11]. Our definitions incorporate the most up-to-date research such as the need to exclude chromosomal integration before confirming HHV-6 as the definitive cause [18]. As a third of all acute encephalitides are thought be immune-mediated and often the distinction from acute infectious encephalitis cannot be made on clinical grounds alone, it is crucial to include non-infectious causes in any case definitions for acute encephalitis.

Yet other studies in North America have based their criteria solely on the type of specimen in which the organism was detected [19, 20]. Other studies have not made the criteria they used explicit. In one study, prior to the routine use of molecular diagnostics, causative agents were assigned by isolation of the organism from the nasopharynx [21]. The fact that so many case definitions are used, and that they are of such varying quality, makes comparison between existing studies difficult.

This paper is an important addition to the limited literature available on case definitions of encephalitis. Encephalitis is of global public health concern and as a result numerous studies are either underway or being planned. Achieving consensus for these aetiological case definitions will facilitate comparison between studies and ultimately result in a better understanding of the causes of this devastating neurological condition. They provide a framework for regular review and updating as the knowledge base increases both clinically and through improvements in diagnostic methods, while the importance of new and emerging pathogens as causes of encephalitis can be assessed against the principles laid out here.

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DECLARATION OF INTEREST

None.

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