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# The Value of Standardized Case Definitions in Encephalitis Clinical Research

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## 1. Introduction

Encephalitis is a poorly defined disease entity. Encephalitic symptoms may be vague and unspecific, especially in the neonatal and pediatric age groups. Early signs and symptoms such as fever, malaise, headache and fatigue are fairly common and shared with many disease entities, infectious and non-infectious. Even if neurologic symptoms prevail and an encephalitis diagnosis has moved to the top of the list of differential diagnoses, overlap with other disease entities remains a possibility - in particular with meningitis, cerebellitis, myelitis and acute disseminated encephalomyelitis (ADEM).

Encephalitis appears to be under-diagnosed and in the majority of cases of encephalitis, the pathogen or cause remain unknown.[1-5] Furthermore, surveillance programs in Scandinavia revealed that 60% of the children with encephalitis had persisting symptoms at the time of discharge. Systematic evidence-based research and prospective surveillance are warranted to learn more about the clinical spectrum, underlying causes, and prognostic factors of encephalitis. The ultimate goal of encephalitis clinical research should be to improve treatment modalities and disease outcomes in all patients, regardless of age and geographic background.

Meaningful epidemiologic investigations of encephalitis disease outcomes, incidence and prevalence require large-scale studies, multi-centric approaches, and the pooling and meta-analysis of significant amounts of data from different parts of the world. For data comparability purposes, pre-defined standards should be used for the inclusion of patients into encephalitis surveillance cohorts. Inclusion criteria for encephalitis studies should be based on observer-independent, widely accepted clinical case definitions and ideally, international consensus.

This paper aims to raise awareness of the challenges of defining and diagnosing encephalitis as a disease entity, while presenting a number of practical approaches to facilitate encephalitis screening for pediatric clinical research and public health purposes.

## 2. Problem

Very few large-scale studies have been conducted to date monitoring the incidence and prevalence of encephalitis, and even fewer targeting the paediatric age group. Usually, these studies are set up as laboratory-based investigations or with a specific disease entity or pathogen in mind such as West Nile Virus[6], Japanese Encephalitis Virus (JEV), tick borne encephalitis (TBE), rotavirus, varicella and other herpesviruses.

Examples of key topics in encephalitis studies in recent years are:

- The early detection of congenital encephalitis and TORCH infections
- Regional and periodic epidemiologic surveillance of arbovirus infections
- Polio surveillance (WHO)
- Baseline prevalence of vaccine preventable disease
- Monitoring of adverse events following immunization (AEFI)

**Example 1: The discussion around Rotavirus Encephalitis/ Encephalopathy**

Ever since the first cases of CNS involvement in rotavirus disease were reported, it has been discussed if and when one of the most common pathogens causing gastroenteritis in children under the age of 4 may also cause neurologic symptoms and complications. Table 1 illustrates a summary of the first case reports of rotavirus encephalitis in the medical literature.

| Case, Reference | Location | Year | Age | Sex | Neurological Diagnosis | Stool | CSF | Blood | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1. Salmi et al. [7] | Finland | 1978 | 2 yr | F | Seizures | EM | | | Patient died |
| 2. Salmi et al. [7] | Finland | 1978 | 3 yr | F | Seizures | EM | | NCDV | Slow recovery |
| 3. Wong et al. [8] | USA | 1984 | 6 mo | M | Aseptic meningitis | EIA, IEM | EIA, IEM, pleocytosis | | Healthy |
| 4. Ushijima et al. [9] | Japan | 1986 | 9 mo | M | Acute encephalitis | PAGE, Latex agglutination (LA), EM, RV IgA | RV IgG, IgA, IgM | RV IgG, IgA, IgM, CFT | Coma x 10 d, infantile spasms, developmental delay |
| 5. Keidan et al. [10] | Israel | 1992 | 2 yr | M | Encephalopathy | EIA | EM | | Healthy |
| 6. Keidan et al.[10] | Israel | 1992 | 21 mo | M | Encephalopathy | EIA | | | Healthy |
| 7. Yoshida et al.[11] | Japan | 1995 | 2 yr | F | Encephalitis | Latex agglutination (LA) | RT-PCR, pleocytosis | | Healthy |
| 8. Pang et al. [12] | Finland | 1996 | 9 mo | F | Febrile seizures | EIA, RT-PCR | RT-PCR | RT-PCR, RV IgG, IgA | Healthy |
| 9. Makino et al. [13] | Japan | 1996 | 21 mo | F | Encephalopathy | EIA, RT-PCR | RT-PCR | RT-PCR, CFT | Hemiparesis, mental retardation |
| 10. Hongou et al.[14] | Japan | 1998 | 2 yr | M | Encephalitis | LA | RT-PCR, RV IgG, pleocytosis | CFT | Healthy |
| 11. Pager et al.[15] | South Africa | 2000 | 1yr | M | Seizures | LA | RT-PCR | | Pat. died first day of life |
| 12. Lynch et al. [16] | USA | 2001 | 6 yr | M | Seizures | EIA | RT-PCR | RV IgA | Pat. died after 5 mo |
| 13. Lynch et al. [16] | USA | 2001 | 2.5 yr | F | Encephalitis | EIA | RT-PCR | | Healthy |
| 14. Goldwater et al. [17] | Australia | 2001 | 2.5 yr | M | Encephalitis | EIA | PCR, RT-PCR | | Slow recovery, sequelae (hypotonia, unclear speach) |
| 15. Goldwater et al. [17] | Australia | 2001 | 13 mo | M | Encephalopathy | EIA | RT-PCR | | Moderate hemiparesis |
| 16. Nigrovic et al. [18] | USA | 2002 | 3 yr | F | Cerebellitis | RT-PCR | RT-PCR | | Wide-base gait, moderate expressive aphasia |

| Case, Reference | Location | Year | Age | Sex | Neurological Diagnosis | Stool | CSF | Blood | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| 17. Morrison[19] | USA | 2001 | 4 yr | | Encephalitis, cerebral edema, uncal herniation | | CNS in situ RT-PCR, in situ hybridization | | Patient died |
| 18. Kobata et al. [20] | Japan | 2002 | 2 yr | F | Encephalopathy | Immunochromatography, EM, RT-PCR | | | Healthy |
| 19. Iturriza-Gomarra et al. [21] | UK | 2002 | 2 yr | M | Seizures | LA, RT-PCR | RT-PCR | | Healthy |
| 20. Kehle et al. [22] | Germany | 2003 | 9 mo | F | Meningo-encephalitis | EIA | RT-PCR, pleocytosis | IgM | Healthy |
| 21. Rath et al.[23] | USA | 2004 | 8 mo | M | Encephalitis | EIA | RT-PCR, probe hybridization | | Mental retardation, dystonia, developmental delay |
| 22. Nakagomi et al.[24] | Japan | 2005 | 1.5 yr | M | | ELISA or LA | | ELISA | |
| 23. Nakagomi et al.[24] | Japan | 2005 | 0.5 yr | M | | ELISA or LA | | ELISA | |
| 24. Nakagomi et al.[24] | Japan | 2005 | 4 yr | F | Not reported in detail. | ELISA or LA | | ELISA | |
| 25. Nakagomi et al.[24] | Japan | 2005 | 3 yr | F | Manifestations included | ELISA or LA | | ELISA | |
| 26. Nakagomi et al.[24] | Japan | 2005 | 2.5 yr | M | encephalitis, encephalopathy, convulsions or seizures. | ELISA or LA | | ELISA | Not reported |
| 27. Nakagomi et al.[24] | Japan | 2005 | 1.5 yr | F | | ELISA or LA | RT-PCR | | |
| 28. Nakagomi et al.[24] | Japan | 2005 | 9 yr | F | | ELISA or LA | RT-PCR | | |
| 29. Nakagomi et al.[24] | Japan | 2005 | 2 yr | F | | ELISA or LA | RT-PCR | | |
| 30. Kirton et al.[25] | Canada | 2005 | 15 mo | F | Necrotizing encephalopathy | EIA | | | Patient died |
| 31. Shiihara et al.[26] | Japan | 2007 | 2.5 yr | F | Encephalitis, Cerebellitis | Immunochromatography, RT-PCR | Pleocytosis (RT-PCR -) | | Slow speech and dysarthria |
| 31. Shiihara et al.[26] | Japan | 2007 | 4.5 yr | M | Encephalitis, Cerebellitis | Immunochromatography | | | Slow speech, dysarthria, hand tremor |
| 32. Furuya et al.[27] | Japan | 2007 | 3.5 yr | F | Encephalitis | RT-PCR | RT-PCR | | Not reported |

Table 1.

Notably, thirty-three cases of rotavirus disease with CNS involvement had been reported up until the time when the new rotavirus vaccines were introduced in the United States. [16-22 25-28] Among these 32 cases, less than half (10/24; 42%) of the patients with reported outcomes recovered completely. Five children (21%) died from the disease, whereas the remaining 37% experienced neurological sequelae. [23]

With increased awareness evidence has since grown further, and CNS involvement is slowly being recognized as a rare but potentially serious complication in rotavirus gastroenteritis.[29-38] Over time, in addition to viral diagnostics radiological features of

rotavirus encephalitis are better understood, which may help in directing clinicians to the correct diagnosis. [23] [37]

During and prior to the time of rotavirus vaccine introduction in different parts of the world, large rotavirus surveillance programs have been instituted. Despite the size and number of such programs, meta-analysis is difficult as very little information can be obtained on rare complications of rotavirus disease. Studies were designed measuring different endpoints and inconsistent criteria and definitions have been applied (if any) for CNS complications.

An exception for surveillance studies of seizures in rotavirus disease:

A subanalysis of a 5- year rotavirus surveillance in Salt Lake City, Utah (2002-6) is a rare exception specifically focusing of CNS complications. Investigators retrospectively identified 34/59 children with laboratory-confirmed rotavirus infection and >=1 seizure without an alternative medical explanation. They reported one child with cerebral edema on neuroimaging and abnormal EEG and 2 children (7%) who required chronic anticonvulsant therapy concluding "…that seizures associated with rotavirus infection are a relatively benign neurologic condition in young children. With few exceptions, neurodiagnostic studies do not influence management or outcome."[39].

Precise data and incidence rates with respect to encephalitis/ encephalopathy in large-scale rotavirus surveillance programs are sill lacking. In the meantime, CNS complications have also been reported in gastroenteritis due to other viruses such as norovirus [40] and adenovirus [41].

**Example 2: Encephalitis as a vaccine preventable disease**

A number of recent encephalitis surveillance studies have been focusing on vaccine preventable disease, such as tick borne encephalitis (TBE) and Japanese encephalitis virus (JEV).

Systematic tick born encephalitis studies have recently been conducted in Eastern European countries where the disease is endemic, such as Slovenia [42], Poland [43], and Latvia [44]. A common European approach has been sought by VENICE (http://venice.cineca.org/final_report_TBE_19-01-2011.pdf) and several others [45, 46, 47] however, universal criteria for the clinical assessment and grading of encephalitis still remain to be implemented.

With respect to Japanese Encepahlitis Virus (JEV), surveillance has recently been extended to many Asian countries including Bangladesh [48], Nepal [49], Japan [48], to name only a few. New WHO criteria for JEV have been defined and evaluated. [50] More recently, general systemativ surveillance programs and monitoring activities preparing the introduction of JEV vaccine have been developed by PATH in Vietnam, and Nepal (http://www.path.org/publications/detail.php?i=1523).

With the introduction of varicella vaccine, varicella zoster virus (VZV) has become the first vaccine preventable disease caused by herpesviridae. Complications of VZV disease include CNS involvement with the clinical picture of encephalitis/cerebellitis. Neurologic complications in VZV infection are common in, but not restricted to immuno-compromized patients [51] and may even occur in the context of reactivation (varicella zoster). [52]

A 1-year surveillance of hospitalizations for VZV complications was conducted in 1997 in 485 German pediatric hospitals including neurologic complications, bacterial superinfections, and hematologic complications (with multiple entries permitted in the surveillance questionnaire). Notably, neurologic complications were among the most

common with 61.3% (in comparison to infectious complications with 38.6%). Among CNS complications, cerebellitis was predominant with 40.3%, followed by encephalitis (18.4%) and meningitis (1.7%) and facial palsy (0.8%). [53] Similar studies have recently been conducted in Italy [54, 55], UK, Ireland, [56] and Saudi Arabia [57].

Parallel to increased efforts in developing a cytomegalovirus (CMV) vaccine [58-61], attention has also shifted to further understanding the neurologic sequelae and disease burden of congenital CMV disease and non-immunocompromised hosts. [62-22]

In addition, influenza has been increasingly recognized as a vaccine preventable cause of encephalitis, especially in children and adolescents. [67] Initial reports emerged from Japan and the United States [68-75] and recently, a number of case reports as well as surveillance reports by CDC have been issued on neurologic complications of Influenza A (in particular pandemic H1N1) disease. [76-88]

**Example 3: Encephalitis as an adverse event following immunization (AEFI)**

Encephalitis has not only been described as a viral and/or immunological illness, but also as an adverse event following immunization (AEFI)[89]. The British Pediatric Surveillance Unit conducted a 3-year prospective surveillance aiming to investigate encephalitis as an AEFI in the UK and Ireland[90]

By nature, AEFI are rare events requiring large-scale studies, meta-analyses, or extensive (ideally active) surveillance programs to be detected. Reporting bias and awareness are major obstacles to the systematic assessment of AEFI. Resent research revealed that physicians are more likely to report a specific AE if the AE constitutes an event a vaccine in designed to prevent. Interestingly, this "reverse placebo effect" also applied to non-live vaccines. [91]

When data have to be pooled from a number of different studies, the use of uniform diagnostic criteria is warranted allowing comparability among studies conducted at different sites. This demand has been met by the Brighton Collaboration, who published a clinical case definition for encephalitis as an AEFI in 2007. [89] The diagnostic criteria for encephalitis as an AEFI are listed in Table 2, below. The Brighton Collaboration criteria are designed to capture an adverse event independent from any potential triggers, but also to differentiate reliably and consistently between different kinds of CNS involvement, including meningitis, meningo-encephalitis, myleitis, ADEM and the like.

The Brighton Collaboration case definitions for aseptic meningitis, encephalitis, myelitis and ADEM have since been evaluated in a retrospective analysis of 255 clinical cases of CNS disease in a Swiss children's hospital. [93] This evaluation study revealed that unless predefined clinical criteria are applied consistently, the demarcation of closely related but distinct CNS disease entities will be missed. ICD-10 coding and diagnoses mentioned in hospital discharge summaries are insufficient and all too often observer-dependent. [93]

**Brighton Collaboration Case Definition for Encephalitis as an AEFI** [89]
**"Case definitions: encephalitis, myelitis, and ADEM"**[1]

**Encephalitis - Level 1 of diagnostic certainty:**[2]

(a) Demonstration of acute inflammation of central nervous system parenchyma (± meninges) by histopathology.

**Encephalitis - Level 2 of diagnostic certainty:**[3,4]

(a) Encephalopathy (e.g. depressed or altered level of consciousness, lethargy, or personality change lasting >24 h),

**AND INCLUDING**

(b) **ONE OR MORE** of the following:
1. Decreased or absent response to environment, as defined by response to loud noise or painful stimuli,
2. Decreased or absent eye contact,
3. Inconsistent or absent response to external stimuli,
4. Decreased arousability,
5. Seizure associated with loss of consciousness.[92]

**OR**

(c) Focal or multifocal findings referable to the central nervous system, including one or more of the following:
1. Focal cortical signs (including but not limited to: aphasia,alexia, agraphia, cortical blindness),
2. Cranial nerve abnormality/abnormalities,[5]
3. Visual field defect/defect(s),
4. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex),
5. Motor weakness (either diffuse or focal; more often focal)[5]
6. Sensory abnormalities (either positive or negative; sensory level),
7. Altered deep tendon reflexes (hypo- or hyperreflexia, reflex asymmetry),
8. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus.

**AND (for both possibilities to reach Level 2)**

(d) TWO OR MORE[6] of the following indicators of inflammation of the CNS:
1. Fever (temperature ≥38° C),
2. CSF pleocytosis (>5WBC/mm3 in children >2 months of age; >15WBC/mm3 in children <2 months of age),
3. EEG findings consistent with encephalitis,[7] or
4. Neuroimaging consistent with encephalitis.[8]

**Encephalitis - Level 3 of diagnostic certainty:**[3,4]

(a) Encephalopathy (e.g. depressed or altered level of consciousness, lethargy, or personality change lasting >24 h),

**AND INCUDING**

(b) **ONE OR MORE** of the following:
1. Decreased or absent response to environment, as defined by response to loud noise or painful stimuli,
2. Decreased or absent eye contact,
3. Inconsistent or absent response to external stimuli,

4. Decreased arousability, or
5. Seizure associated with loss of consciousness. [92]

**OR**

(c) Focal or multifocal findings referable to the central nervous system, including one or more of the following:
1. Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness),
2. Cranial nerve abnormality/abnormalities,[5]
3. Visual field defect/defect(s),
4. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex),
5. Motor weakness (either diffuse or focal; more often focal), [5]
6. Sensory abnormalities (either positive or negative; sensory level),
7. Altered deep tendon reflexes (hypo- or hyperreflexia, reflex asymmetry), or
8. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus.

**AND (for both possibilities to reach Level 3)**

(d) **ONE**[7] of the following indicators of inflammation of CNS:
1. Fever (temperature ≥38°C),
2. CSF pleocytosis (>5WBC/mm3 in children >2 months of age; >15WBC/mm3 in children <2 months of age),
3. EEG findings consistent with encephalitis,[7] or
4. Neuroimaging consistent with encephalitis.[8]

**Encephalitis - Level 3A of diagnostic certainty:**[7,9]

(a) Insufficient information is available to distinguish case between acute encephalitis or ADEM; case unable to be definitively classified.

**Encephalitis - Exclusion criterion for levels 2 and 3 of diagnostic certainty:**

(a) Other diagnosis for illness present.[10]

[2] If the lowest applicable level of diagnostic certainty of the definition for a definitive category (i.e., Level 3, excluding Level 3A) is met and there is evidence that the criteria of the next higher level of diagnostic certainty (Level 2) are met, the event should be classified in the next category. This approach should be continued until the highest level of diagnostic certainty for a given event can be determined. Thus, if a case fits diagnostic criteria for both categories (encephalitis and ADEM), but reaches a higher level of diagnostic certainty in one, the higher level supercedes, and the case should be classified according to the category in which the higher diagnostic certainty level is reached. TheWorking Group recognizes that under this paradigm, it is possible to reach a higher level of diagnostic certainty forADEMwith less stringent criteria than it is for encephalitis e.g., Level 1 diagnostic certainty for encephalitis requires histopathologic diagnosis, whilst ADEM Level 1 does not require this. However, in the absence of a biological marker, the diagnosis of ADEM rests upon the proper neuroimaging findings in the appropriate clinical context, and the combination of appropriate neuroimaging and a monophasic pattern of illness are as close to a gold standard as exist for this clinical entity. Thus, one may have a higher level of diagnostic certainty of ADEM than of encephalitis, in the absence of other biologic data. When Level 1 ADEM and Level 2 encephalitis, or Level 2 ADEM

and

Level 3 encephalitis are met, the best category to choose would be ADEM.

[3] The encephalitis/ADEMWorking Group recognizes that, in most cases, histopathologic examination of tissue will not be practicable as a method of diagnosis; this may particularly be the case in developing countries. However, histopathologic demonstration of cerebral inflammation remains the "gold standard" for the diagnosis of encephalitis, and as such, the group has determined that this should be Level 1 for determination of encephalitis.

[4] Levels 2 and 3 of diagnostics certainty have been especially designed for adults and children older than or equal to 2 years of age. For children under the age of 2 years (and, in particular, those under the age of 6 months) the nervous system and, as such, the neurologic examination is continually in flux (e.g., what is normal in a 28-day old is not necessarily normal in a 2- month old child). The evaluation of encephalopathy and neurologic deficits in infants and young children will need to be done in an age-appropriate fashion, taking into account the age and level of development of the child.

[5] Levels 2 or 3 of encephalitis are met if criteria (a+b+d) or (c+d) from the respective levels are fulfilled, and no exclusion criteria are met.

[6] Note that only criteria 2 and 5 may be applicable in all age groups; other criteria for focal/mulitfocal neurologic signs may be age-dependent, and will not be applicable to all age groups.

[7] Note that Level 2 of diagnostic certainty requires at least 2 of the listed criteria for inflammation, while Level 3 required only 1 criteria. This is in recognition that, in some cases of encephalitis, all listed criteria will either not be present, or such data will be unavailable. Thus, a clinical diagnosis of encephalitis should still be applicable, but will be of less diagnostic certainty than if sufficient criteria were present.

[8] Electroencephalographic (EEG) findings consistent with encephalitis:EEG findings consistent with encephalitis include, but are not limited to: Diffuse or multifocal nonspecific (nonphysiologic) background slowing; periodic discharges or other encephalographic abnormalities may or may not be present.

[9] Neuroimaging findings consistent with encephalitis: Neuroimaging findings consistent with encephalitis include, but are not limited to: head computed tomography (CT) displaying areas of hypodensity; contrast images demonstrating meningeal and parenchymal enhancement indicating meningeal and parenchymal inflammation, or gyral enhancement, brain/spine magnetic resonance imaging (MRI) displaying diffuse or multifocal areas of hyperintense signal on T2-weighted, diffusion-weighted image, or fluid-attenuation inversion recovery (FLAIR) sequences, suggestive of inflammation or demyelination.

Tabe 2. Brighton Collaboration Case Definition for Encephalitis as an AEFI (see www.brightoncollaboration.org)

## 3. Assessment of the problem

Most of the attempts to standardize the diagnosis of encephalitis are focusing on adults whereas pediatric studies are facing specific challenges in the differential diagnosis, such as age-dependent symptoms while intellectual capabilities are still developing and the difficulty to distinguish acute neurologic impairment from consequences of perinatal asphyxia and congenital malformations, developmental delay, intoxication and other alternative possible non-infectious causes of encephalopathy.[2, 5] Due to the immaturity of the immune system and the blood-brain barrier, children under the age of two are at a

particularly high risk of developing encephalitis during bacterial sepsis or systemic infection with herpesviridae, Tb and many other pathogens. At the same time the chance of recurrence of HSV meningo-encephalitis is difficult to assess and consequences of premature discontinuation of antiviral therapy can be detrimental. [94-99] Even in older children, the difficulty to identify symptoms of encephalopathy such as behavioral outbursts, decreased responsiveness, and other subtle signs may delay the diagnosis and thus, treatment. [100, 101] In other cases, the differentiation of autoimmune from viral causes of encephalitis causes problems. [100,4] Without the identification of potential causes of encephalitis, however, the treatment options and prognosis in different types of encephalitis will remain poorly understood.[1, 102]

With additional diagnostic and therapeutic options becoming available, and several types of encephalitis vaccine-preventable, the systematic surveillance of encephalitis in children has gained significance, also with respect to everyday clinical care.

As indicated above, prospective and retrospective case ascertainment both provide a number of challenges. Prospective surveillance of large cohorts using predefined case definitions is key to avoid inter-rater variability and selection bias. The installment of active surveillance systems in specialized reference centers will ultimately improve the monitoring of encephalitis as an AEFI. Children with acute CNS adverse events are most likely to present in emergency rooms and tertiary care centers rather than private pediatric practices, where the child has usually been immunized. Unless immunizations are systematically captured at the time of investigation, rates of encephalitis and other CNS adverse events following immunization - as opposed to other triggers or causes - can hardly be established. [90, 103] In addition, lumbar puncture is difficult to perform in infants and children, and even if CSF has been obtained, pathogens other than HSV and bacteria are rarely assessed in routine practice. Very little is known for example, about incidence rates of enterovirus infection in pediatric CNS disease.[104] However, effective enterovirus surveillance can also be utilized as a tool for regional polio disease surveillance, as is the case at the German National Reference Laboratory for Enteroviruses at the Robert Koch Institute in Berlin.[105, 106]

Hospital-based prospective surveillance systems have been introduced in several locations, including country-wide surveillance systems in the US[4], France[107], the UK [2] and Sweden [1], as well as smaller programs in Taiwan [108], Crete [109], and India.[110] Unfortunately, each of these programs use their own case definitions for encephalitis.

Table three provides several examples of clinical case definitions used in recent pediatric encephalitis studies:

| First Author | Title | Country | Type/Category | Year(s) of Study | Clinical Case Definition for Encephalitis |
|---|---|---|---|---|---|
| Amin [67] | Acute childhood encephalitis and encephalopathy associated with influenza: a prospective 11-year review | Canada | Influenza Encephalitis | 1994 - 2004 | "Encephalopathy was defined as a depressed or altered level of consciousness persisting for 24 hours. Encephalitis was defined by the presence of encephalopathy plus 2 or more of the following criteria: fever (temperature 38.0°C), seizure(s), focal neurologic findings, cerebrospinal fluid (CSF) pleocytosis (WBC count 5 106 cells/L), EEG findings compatible with encephalitis, or abnormal neuroimaging" |

| First Author | Title | Country | Type/Category | Year(s) of Study | Clinical Case Definition for Encephalitis |
|---|---|---|---|---|---|
| Anga [111] | The aetiology, clinical presentations and outcome of febrile encephalopathy in children in Papua New Guinea | Papua New Guinea | Febrile Encephalo-pathy | ND | "Children aged between 1 month and 12 years presenting to Port Moresby General Hospital with febrile encephalopathy, defined as fever, seizures and/or altered consciousness" |
| Beig [110] | Etiology and clinico-epidemiological profile of acute viral encephalitis in children of western Uttar Pradesh, India | India | Acute viral encephalitis | Jul 2004-Nov 2006 | "Acute encephalopathy was defined as fever with alteration of consciousness and/or with neurological deficit, secondary to central nervous system involvement lasting more than 24 hours, and not more than a oneweek history. Patients with a different final diagnosis (e.g., epilepsy, febrile convulsion, bacterial meningitis, tuberculosis, brain tumor, cerebral malaria, or metabolic disorder) were excluded from the study." |
| Elbers [112] | A 12-year prospective study of childhood herpes simplex encephalitis: is there a broader spectrum of disease? | USA | HSV Encephalitis | 1994-2005 | "Inclusion criteria for this registry are documented encephalopathy, defined as depressed or altered level of consciousness persisting for >24 hours, plus 2 of the following: fever (>38°C), seizure, focal central nervous system (CNS) findings, CSF pleocytosis (>5 x 106 cells per L), EEG abnormalities, or diagnostic imaging abnormalities (on brain computed tomography [CT]/MRI scans). Patients were excluded if they had underlying neurologic disease or were known to have immunosuppression. This study did not include cases of neonatal encephalitis and focused on children between 4 weeks and 18 years of age. For identification of a cohort of children with clinically and diagnostically definite HSE, patients in our study fulfilled stringent inclusion criteria: the aforementioned criteria of the encephalitis registry, CSF PCR and/or serologic evidence of HSV infection, and 1 of the following: CSF abnormalities, including the presence of pleocytosis, >50 x 106 red blood cells (RBCs) per L, and/or elevated protein levels (>0.4 g/L), EEG readings consistent with HSE, or CT and MRI findings suggesting HSE, such as focal signal abnormalities or hemorrhage. Patients were excluded if an alternative diagnosis accounted for their symptoms." |

| First Author | Title | Country | Type/Category | Year(s) of Study | Clinical Case Definition for Encephalitis |
|---|---|---|---|---|---|
| Fowler [1] | Childhood encephalitis in Sweden: etiology, clinical presentation and outcome | Sweden | Encephalitis | 2000-2004 | A. Age 1 month–18 years<br>B. Signs of cerebral dysfunction either as.<br>1. encephalopathy defined as altered consciousness, personality or behavioral changes lasting for more than 24 hr, or 2. abnormal EEG finding compatible with encephalitis, plus at least one of the following: - Abnormal results of neuroimaging compatible with encephalitis, -Positive focal neurological findings, -Seizures.<br>C. Signs of inflammation, defined either as pleocytosis (X6 white blood cells/mL), fever (38C) or elevated infectious parameters (CRP,WBC). Mild symptoms from eyes, nose or throat were not considered to be sufficient." |
| Ganerod [2] | Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study | UK | Encephalitis | Oct 2005-Nov 2006 | "The case definition included any person of any age admitted to hospital with encephalopathy (altered consciousness that persisted for longer than 24 h, including lethargy, irritability, or a change in personality and behaviour) and with two or more of the following:fever or history of fever (≥38ºC) during the presenting illness; seizures and/or focal neurological fi ndings (with evidence of brain parenchyma involvement); CSF pleocytosis (more than four white blood cells per µL); electroencephalographic (EEG) fi ndings indicative of encephalitis; and abnormal results of neuroimaging (CTor MRI) suggestive of encephalitis." |
| Glaser [113] | In search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project, 1998-2000 | USA | Encephalitis | 1998-2000 | "A case was defined as encephalopathy (depressed or altered level of consciousness lasting<br>24 h, lethargy, or change in personality) requiring hospitalization with 1 of the following symptoms: fever, seizure, focal neurological findings, CSF pleocytosis, or electroencephalography or neuroimaging findings consistent with encephalitis.", > 6 months of age |
| Glaser [4] | Beyond viruses: clinical profiles and etiologies associated with encephalitis. | USA | Encephalitis | 1998 -2005 | ">= 6 months of age, and met the CEP case definition of encephalitis. A "case patient" was defined as a patient hospitalized with encephalopathy (defined by a depressed or altered sonality change) with level of consciousness lasting 24 h, lethargy, or a per 1 of the following characteristics: fever, seizure, focal neurological findings, pleocytosis, or electroencephalography or neuroimaging findings consistent with encephalitis." |

| First Author | Title | Country | Type/Category | Year(s) of Study | Clinical Case Definition for Encephalitis |
|---|---|---|---|---|---|
| Ward [90] | Risk of Serious Neurologic Disease After Immunization of Young Children in Britain and Ireland | Britain and Ireland | Immunization | | "Case definiton of serious neurologic disease: children 2 to 35 month with suspected encephalitis and/or severe illness with fever and convulsions. Convulsion: total duration of >30 min OR followed by encephalopathy of 2-23h OR followed by paralysis or other neurological signs not previously present for ≥24h. Fever: ≥37.5°C. Encephalopathy: depressed or altered level of consciousness. Encephalitis: Encephalopathy for ≥24h and TWO of the following: fever, convulsions, focal neurological findings (≥24h), pleocystosis (>5 leucocytes per µl CSF), characteristic abnormal results of neuroimaging (CT or MRI), herpes simplex virus nucleis acid (or nucleic acid of any other virus proven to cause encephalitis) in CSF; OR postmortem histologic evidence of encephalitis. Exclusion criteria: viral meningitis without encephalopathy; the following confirmed causes: hypoxic/ischemic; vascular; toxic; metabolic, neoplastic, traumatic, pyogenic infections; uncomplicated convulsions or a series of convulsions lasting 30 min; immunocompromised children." |
| Hossain [48] | Hospital-based surveillance for Japanese encephalitis at four sites in Bangladesh, 2003-2005. | Bangladesh | Japanese Encephalitis | 2003-2005 | ".. clinical case definition of acute encephalitis with indication for lumbar puncture, based on the judgment of the patient's attending physician. The clinical case definition of acute encephalitis included new onset of fever (temperature > 38°C) or history of fever during the present illness along with altered mental status, (e.g., confusion, disorientation, coma) and/or a neurological deficit (i.e., focal or diffuse neurological dysfunction or new onset of seizures) with onset of the neurological symptoms within five days prior to hospitalization. Enrollment in the study required that the patient met the clinical case definition and that he or she had cerebrospinal fluid (CSF) pleocytosis (defined as > 4 leukocytes/mm3 for patients > 6 weeks of age and > 14 leukocytes/mm3 for the patients > 6 weeks of age)..." |
| Huang [102] | Long-term cognitive and motor deficits after enterovirus 71 brainstem encephalitis in children | Taiwan | Enterovirus Encephalitis | 1998 - 2004 | "case definition for enterovirus 71 brainstem encephalitis: myoclonus, ataxia, nystagmus, oculomotor palsies, and bulbar palsy, in various combinations, with or without confirmation by neuroimaging". |

| First Author | Title | Country | Type/Category | Year(s) of Study | Clinical Case Definition for Encephalitis |
|---|---|---|---|---|---|
| Le [3] | Viral etiology of encephalitis in children in southern Vietnam: results of a one-year prospective descriptive study | Vietnam | Encephalitis | Jan-Dec 2004 | "Children admitted [..] with suspected acute encephalitis of viral origin, based on the clinical judgment of admitting physicians, and with no preexisting neurological conditions or evidence of bacterial meningitis by microscopy or culture of cerebrospinal fluid (CSF) samples, and no febrile convulsion (defined by a single convulsion lasting less than 15 minutes with regaining of consciousness within 60 minutes in a child between 6 months and 6 years of age) were eligible for inclusion in the study after provision of written informed consent by the patient's parents or legal guardians" |
| Lee [108] | Encephalitis in Taiwan: a prospective hospital-based study | Taiwan | Encephalitis | 2000-2001 | "Encephalitis was defined as follows: acute and severe neurological dysfunction in the context of suspected encephalitis, which included signs and symptoms of acute mental dysfunction, memory impairment, LOC, pareses, abnormal behaviour, convulsions, and involuntary movement. The patient's EEG and/or CT scan and LP were also compatible with the diagnosis of encephalitis. Patients with high fever, headache, nausea and vomiting were excluded by LP, CT/MRI or EEG examination. Patients with other diseases, especially with other systemic infection (sepsis), cerebral vascular accident, neoplasm of the brain or psychiatric diseases that caused disturbed consciousness were also excluded by LP, CT/MI or EEG examination." |
| Mailles [107] | Infectious encephalitis in France in 2007: a national prospective study | France | Encephalitis | Jan-Dec 2007 | "Inclusion criteria: age ≥ 28 days hospitalized in mainland France in 2007 AND (1) acute onset of illness, (2) at least 1 abnormality of the CSF (white blood cell count of ≥ 4 cells/mm³ OR protein level of ≥ 40mg/dl), (3) temperature ≥ 38°C, (4) decreased consciousness OR seizures OR altered mental status OR focal neurologic signs. Exclusion criteria: hospitalization of fewer than 5 days (to avoid including patients with aseptic meningitis without brain involvement), positive HIV status, meningitis without clinical brain involvement, brain abscess, prion disease, cerebral malaria, non-infectious CNS-disease" |
| Morishima [114] | Encephalitis and encephalopathy associated with an influenza epidemic in Japan | Japan | Influenza Encephalitis | winter of 1998–1999 | "The diagnosis of encephalitis/ encephalopathy was made on the basis of all clinical signs. All patients had altered consciousness or loss of consciousness. Patients with meningitis, myelitis, and febrile convulsions without prolonged unconsciousness were excluded. Postictal unconsciousness with prompt recovery was classified as febrile convulsion" |

| First Author | Title | Country | Type/Category | Year(s) of Study | Clinical Case Definition for Encephalitis |
|---|---|---|---|---|---|
| Olsen [115] | Japanese encephalitis virus remains an important cause of encephalitis in Thailand | Thailand | Encephalitis | 2003-2005 | "the following criteria were approached for enrollment: (1) fever or hypothermia (i.e., history of fever or documented temperature 38 8C or 35 8C); (2) evidence of acute brain dysfunction (i.e., encephalopathy, central neurological findings, or seizures) with onset 14 days prior to admission; and (3) clinical indication for lumbar puncture as determined by a staff physician." |
| Schubart [116] | Short report: Role of viruses in Kenyan children presenting with acute encephalopathy in a malaria-endemic area | Kenya | Cerebral Malaria | 1999-2001 | "Differenciation between cerebral malaria, bacterial meningitis and viral encephalitis. Cerebral malaria: WHO definition. Bacterial meningitis confirmed by the examination and culture of CSF. Viral encephalitis confirmed by looking for evidence of herpesviruses and enteroviruses." |
| Solomon [50] | A cohort study to assess the new WHO Japanese encephalitis surveillance standards | Viet Nam | Japanese Encephalitis | Jan-Dec 1995 | "Clinically, a case of acute encephalitis syndrome (AES) is defined as a person of any age, at any time of year, with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) AND/OR new onset of seizures (excluding simple febrile seizures).[a] Other early clinical findings can include an increase in irritability, somnolence or abnormal behaviour greater than that seen with usual febrile illness." |
| Ward [90] | Risk of serious neurologic disease after immunization of young children in Britain and Ireland | UK and Ireland (British Pediatric Surveillance Unit) | Encephalitis and Severe Illness with Convulsions and Fever | Oct 1998 - Sept 2001 | "pediatricians were requested to report all children 2 to 35 months old with suspected encephalitis and/or severe illness with fever and convulsions- -> anaöytical case definition: Fever: temperature of 37.5°C; the questionnaire asked whether there was a fever and also for the maximum temperature recorded at any site by any method. Encephalopathy: a depressed or altered level of consciousness. Case definition of serious neurologic disease: any child 2–35 mo old with a severe illness with fever and convulsions (a) and/or encephalitis (b) was included. (a) Severe illness with fever and convulsions: (i) with a total duration of 30 min; or (ii) followed by encephalopathy for 2–23 h; or (iii) followed by paralysis or other neurologic signs not previously present for 24 h. (b) Encephalitis as adapted from [117].(i) Encephalopathy for 24 h and 2 of the following:fever, convulsions, focal neurologic findings ( 24 h), pleocytosis ( 5 leukocytes per L CSF), characteristic |

| First Author | Title | Country | Type/Category | Year(s) of Study | Clinical Case Definition for Encephalitis |
|---|---|---|---|---|---|
| | | | | | abnormal results of neuroimaging (CT or MRI), herpes simplex virus nucleic acid (or nucleic acid of any other virus proven to cause encephalitis) in CSF; or (ii) postmortem histologic evidence of encephalitis. (c) Exclude (i) viral (aseptic) meningitis without encephalopathy (ii) the following confirmed causes were excluded: hypoxic/ischemic; vascular; toxic; metabolic, neoplastic, traumatic, and pyogenic infections (iii) uncomplicated convulsions or a series of convulsions lasting 30 min (iv) immunocompromised children" |

Table 3. Examples of encephalitis surveillance systems and clinical case definitions used.

## 4. Summary and future perspectives

In conclusion, it may be stated that

- prospective surveillance systems for encephalitis have been developed in several sites
- universal case definitions or inclusion criteria are currently not being applied
- clinical encephalitis case definitions are usually not adjusted to age
- a large number of prospective studies are laboratory-based with clinical information added after the fact
- evidence-based information on the multiple causes of encephalitis only slowly emerging.

With the emergence of surveillance systems for encephalitis worldwide, it would be desirable to introduce the use of uniform case definitions and clinical criteria allowing meta-analysis and head-to-head comparisons between studies and sites. As a first step into this direction, a model surveillance system has been introduced in the pediatric emergency rooms at Charité University Medical Center in Berlin in collaboration with the adjacent Robert Koch Institute, as a first cohort to prospectively implement the neurologic case definitions by the Brighton Collaboration while assessing vaccine preventable neurologic disease along with neurologic adverse events following immunization in the same population.

**The Charité Meningitis Surveillance at Charité (MenSCh ) Cohort: Prospective Surveillance Systems for CNS inflammation and natural infection.**

At Charité, a prospective surveillance system has been put in place monitoring acute presentations of children and adolescents to one of the largest pediatric ERs in Europe. The ERs are located in two different areas of Berlin representing an ethnically diverse population, including up to 40% of children with migratory background (Turkish, Kurdish, Arab/North African, Eastern European). All patients fulfilling predefined case definitions while presenting on regular screening days are automatically enrolled, tested immediately in close collaboration with epidemiologists and the adjacent Robert Koch Institute and followed-up clinically. In the absence of an HMO system in most European countries, this is a powerful method to capture a comprehensive sample of a typical pediatric urban tertiary

care population with "naturally occurring infection" and adverse events. Precise immunization histories are taken at the time of presentation. Case-control and other methodology can be used to compensate for lack of randomization. The **MenSCh (Meningitis Surveillance at Charité) Cohort** is a prospective cohort of children presenting with signs and symptoms of CNS inflammation/infection to the ER. Presentations are classified according to age-adjusted clinical and disease severity scores, but also classified according to standardized case definitions for meningitis, encephalitis, myelitis, ADEM, GBS, seizure and Bell's Palsy by the Brighton Collaboration. Confirmed clinical cases according to the definitions of the Brighton Collaboration, regardless of the trigger (infection, immunization, autoimmune disease), are followed until discharge. Again, detailed immunization histories and laboratory data are captured. After case ascertainment according to standardized case definitions, patients presenting with rare autoimmune AE following immunization will be studied in detail.

Vaccines are among the most effective methodologies available to date for the prevention of infectious diseases of childhood. With declining vaccine acceptance in many parts of the world, it will become increasingly important to learn more about the causes of neurologic adverse events in children. It is hoped that the MenSch cohort will provide a useful contribution to the field while monitoring incidences of vaccine preventable disease alongside with adverse events following immunization.

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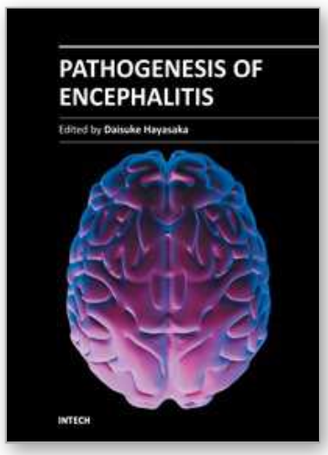
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**Pathogenesis of Encephalitis**
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Many infectious agents, such as viruses, bacteria, and parasites, can cause inflammation of the central nervous system (CNS). Encephalitis is an inflammation of the brain parenchyma, which may result in a more advanced and serious disease meningoencephalitis. To establish accurate diagnosis and develop effective vaccines and drugs to overcome this disease, it is important to understand and elucidate the mechanism of its pathogenesis. This book, which is divided into four sections, provides comprehensive commentaries on encephalitis. The first section (6 chapters) covers diagnosis and clinical symptoms of encephalitis with some neurological disorders. The second section (5 chapters) reviews some virus infections with the outlines of inflammatory and chemokine responses. The third section (7 chapters) deals with the non-viral causative agents of encephalitis. The last section (4 chapters) discusses the experimental model of encephalitis. The different chapters of this book provide valuable and important information not only to the researchers, but also to the physician and health care workers.

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