

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



The Value of Standardized Case Definitions in Encephalitis Clinical Research

Barbara Rath

*Department of Pediatrics, Division of Pneumonology-Immunology,
Charité University Medical Center, Berlin
Germany*

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 Virus⁶, 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 speech)
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 hybridizati on		Patient died
18. Kobata et al. ²⁰	Japan	2002	2 yr	F	Encephalopathy	Immunoch romatogra phy, 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 hybridizati on		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	Immunoch romatogra phy, RT- PCR	Pleocytosis (RT-PCR -)		Slow speech and dysarthria
31. Shiihara et al. ²⁶	Japan	2007	4.5 yr	M	Encephalitis, Cerebellitis	Immunoch romatogra phy			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 still lacking. In the meantime, CNS complications have also been reported in gastroenteritis due to other viruses such as norovirus⁴⁰ and adenovirus⁴¹.

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 Slovenia⁴², Poland⁴³, and Latvia⁴⁴. 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 Encephalitis Virus (JEV), surveillance has recently been extended to many Asian countries including Bangladesh⁴⁸, Nepal⁴⁹, Japan⁴⁸, to name only a few. New WHO criteria for JEV have been defined and evaluated.⁵⁰ More recently, general systematic 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 patients⁵¹ 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 Arabia⁵⁷.

Parallel to increased efforts in developing a cytomegalovirus (CMV) vaccine⁵⁸⁻⁶¹, 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 States⁶⁸⁻⁷⁵ 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 Ireland⁹⁰

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. Recent 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, myelitis, 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 AEFI⁸⁹

“Case definitions: encephalitis, myelitis, and ADEM”¹

Encephalitis - Level 1 of diagnostic certainty:²

(a) Demonstration of acute inflammation of central nervous system parenchyma (\pm 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 $\geq 38^{\circ}\text{C}$),
2. CSF pleocytosis ($>5\text{WBC}/\text{mm}^3$ in children >2 months of age; $>15\text{WBC}/\text{mm}^3$ 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 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, 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 $\geq 38^{\circ}\text{C}$),
2. CSF pleocytosis ($>5\text{WBC}/\text{mm}^3$ in children >2 months of age; $>15\text{WBC}/\text{mm}^3$ 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. The Working Group recognizes that under this paradigm, it is possible to reach a higher level of diagnostic certainty for ADEM with 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/ ADEM Working 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/ multifocal 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.

Tab2. 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 US⁴, France¹⁰⁷, 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	<p>"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.</p> <p>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."</p>

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 B. Signs of cerebral dysfunction either as: 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. 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 (≥38°C) 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 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		<p>“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), pleocytosis (>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.”</p>
Hossain ⁴⁸	Hospital-based surveillance for Japanese encephalitis at four sites in Bangladesh, 2003-2005.	Bangladesh	Japanese Encephalitis	2003-2005	<p>".. 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)..."</p>
Huang ¹⁰²	Long-term cognitive and motor deficits after enterovirus 71 brainstem encephalitis in children	Taiwan	Enterovirus Encephalitis	1998 - 2004	<p>"case definition for enterovirus 71 brainstem encephalitis: myoclonus, ataxia, nystagmus, oculomotor palsies, and bulbar palsy, in various combinations, with or without confirmation by neuroimaging".</p>

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/mm ³ 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	"Differentiation 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.

5. Acknowledgements

The authors kindly thank Ewelina Türk and Jörg Seckinger for their assistance with subsections of the literature review and colleagues at the National Reference Laboratory for Enteroviruses at the Robert Koch Institute in Berlin, for their active collaboration in the development of the MenSch Cohort.

6. References

- [1] Fowler A, Stodberg T, Eriksson M, Wickstrom R. Childhood encephalitis in Sweden: etiology, clinical presentation and outcome. *Eur J Paediatr Neurol* 2008;12(6):484-90.
- [2] Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis* 2010;10(12):835-44.
- [3] Le VT, Phan TQ, Do QH, Nguyen BH, Lam QB, Bach VC, et al. Viral etiology of encephalitis in children in southern Vietnam: results of a one-year prospective descriptive study. *PLoS Negl Trop Dis* 2010;4(10):e854.
- [4] Glaser CA, Honarmand S, Anderson LJ, Schnurr DP, Forghani B, Cossen CK, et al. Beyond viruses: clinical profiles and etiologies associated with encephalitis. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 2006;43(12):1565.
- [5] Stahl JP, Mailles A. Infectious causes of encephalitis. *Lancet Infect Dis* 2010;10(12):814-5.
- [6] Ulbert S. West nile virus: the complex biology of an emerging pathogen. *Intervirology* 2011;54(4):171-84.

- [7] Salmi TT, Arstila P, Koivikko A. Central nervous system involvement in patients with rotavirus gastroenteritis. *Scand J Infect Dis* 1978;10(1):29-31.
- [8] Wong CJ, Price Z, Bruckner DA. Aseptic meningitis in an infant with rotavirus gastroenteritis. *Pediatr Infect Dis* 1984;3(3):244-6.
- [9] Ushijima H, Bosu K, Abe T, Shinozaki T. Suspected rotavirus encephalitis. *Archives of Disease in Childhood* 1986;61(7):692.
- [10] Keidan I, Shif I, Keren G, Passwell JH. Rotavirus encephalopathy: evidence of central nervous system involvement during rotavirus infection. *Pediatr Infect Dis J* 1992;11(9):773-5.
- [11] Yoshida A, Kawamitsu T, Tanaka R, Okumura M, Yamakura S, Takasaki Y, et al. Rotavirus encephalitis: detection of the virus genomic RNA in the cerebrospinal fluid of a child. *Pediatr Infect Dis J* 1995;14(10):914-6.
- [12] Pang XL, Joensuu J, Vesikari T. Detection of rotavirus RNA in cerebrospinal fluid in a case of rotavirus gastroenteritis with febrile seizures. *Pediatr Infect Dis J* 1996;15(6):543-545.
- [13] Makino M, Tanabe Y, Shinozaki K, Matsuno S, Furuya T. Haemorrhagic shock and encephalopathy associated with rotavirus infection. *Acta Paediatr* 1996;85(5):632-4.
- [14] Hongou K, Konishi T, Yagi S, Araki K, Miyawaki T. Rotavirus encephalitis mimicking afebrile benign convulsions in infants. *Pediatr Neurol* 1998;18(4):354-7.
- [15] Pager C, Steele D, Gwamanda P, Driessen M. A neonatal death associated with rotavirus infection--detection of rotavirus dsRNA in the cerebrospinal fluid. *S Afr Med J* 2000;90(4):364-5.
- [16] Lynch M, Lee B, Azimi P, Gentsch J, Glaser C, Gilliam S, et al. Rotavirus and Central Nervous System Symptoms: Cause or Contaminant? Case Reports and Review. *Clinical Infectious Diseases* 2001;33(7):932-938.
- [17] Goldwater PN, Rowland K, Power R, Thesinger M, Abbott K, Grieve A, et al. Rotavirus encephalopathy: Pathogenesis reviewed. *Journal of Paediatrics and Child Health* 2001;37(2):206-209.
- [18] Nigrovic LE, Lumeng C, Landrigan C, Chiang VW. Rotavirus Cerebellitis? *Clinical Infectious Diseases* 2002;34(1):130-130.
- [19] Morrison C, Gilson T, Nuovo GJ. Histologic distribution of fatal rotaviral infection: An immunohistochemical and reverse transcriptase in situ polymerase chain reaction analysis. *Human Pathology* 2001;32(2):216-221.
- [20] Kobata R, Tsukahara H, Nakai A, Tanizawa A, Ishimori Y, Kawamura Y, et al. Transient MR signal changes in the splenium of the corpus callosum in rotavirus encephalopathy: value of diffusion-weighted imaging. *J Comput Assist Tomogr* 2002;26(5):825-828.
- [21] Iturriza-Gomara M, Auchterlonie IA, Zaw W, Molyneaux P, Desselberger U, Gray J. Rotavirus gastroenteritis and central nervous system (CNS) infection: characterization of the VP7 and VP4 genes of rotavirus strains isolated from paired fecal and cerebrospinal fluid samples from a child with CNS disease. *J Clin Microbiol* 2002;40(12):4797-9.

- [22] Kehle J, Metzger-Boddien C, Tewald F, Wald M, Schuurmann J, Enders G. First case of confirmed rotavirus meningoencephalitis in Germany. *Pediatr Infect Dis J* 2003;22(5):468-70.
- [23] Rath B, Gentsch J, Seckinger J, Ward K, Deputy S. Rotavirus encephalitis with basal ganglia involvement in an eight-month old infant. *Clinical Pediatrics* 2011;in press.
- [24] Nakagomi T, Nakagomi O. Rotavirus antigenemia in children with encephalopathy accompanied by rotavirus gastroenteritis. *Archives of Virology* 2005;150(9):1927-1931.
- [25] Kirton A, Busche K, Ross C, Wirrell E. Acute necrotizing encephalopathy in caucasian children: two cases and review of the literature. *J Child Neurol* 2005;20(6):527-32.
- [26] Shiihara T, Watanabe M, Honma A, Kato M, Morita Y, Ichiyama T, et al. Rotavirus associated acute encephalitis/encephalopathy and concurrent cerebellitis: Report of two cases. *Brain Dev* 2007;29(10):670-673
- [27] Furuya Y, Katayama T, Miyahara K, Kobayashi A, Funabiki T. Detection of the rotavirus a genome from the cerebrospinal fluid of a gastroenteritis patient: a case report. *Jpn J Infect Dis* 2007;60(2-3):148-9.
- [28] Wong V. Acute gastroenteritis-related encephalopathy. *J Child Neurol* 2001;16(12):906-10.
- [29] Dickey M, Jamison L, Michaud L, Care M, Bernstein DI, Staat MA. Rotavirus meningoencephalitis in a previously healthy child and a review of the literature. *The Pediatric infectious disease journal* 2009;28(4):318.
- [30] Fukuda S, Kishi K, Yasuda K, Sejima H, Yamaguchi S. Rotavirus-associated encephalopathy with a reversible splenial lesion. *Pediatric Neurology* 2009;40(2):131-133.
- [31] Hickey PW, DiFazio MP. Management of Neurologic Complications of Rotavirus. *The Pediatric infectious disease journal* 2009;28(10):935.
- [32] Incecik F, Herguner MO, Altunbasak S, Solgun H. Acute encephalopathy associated rotavirus gastroenteritis. *Journal of Pediatric Neurosciences* 2009;4(2):141.
- [33] Kato Z, Oori KE, Morimoto M, Sasai H, Funato M, Sawatari S, et al. A transient lesion in the corpus callosum during rotavirus infection. *Pediatric Neurology* 2009;41(6):467.
- [34] Liu B, Fujita Y, Arakawa C, Kohira R, Fuchigami T, Mugishima H, et al. Detection of rotavirus RNA and antigens in serum and cerebrospinal fluid samples from diarrheic children with seizures. *Jpn. J. Infect. Dis* 2009;62(4):279-283.
- [35] Jang YY, Lee KH. Transient splenial lesion of the corpus callosum in a case of benign convulsion associated with rotaviral gastroenteritis. *Korean Journal of Pediatrics* 2010;53(9):859-862.
- [36] Kobayashi S, Negishi Y, Ando N, Ito T, Nakano M, Togari H, et al. Two patients with acute rotavirus encephalitis associated with cerebellar signs and symptoms. *European journal of pediatrics* 2010.
- [37] Takanashi J, Miyamoto T, Ando N, Kubota T, Oka M, Kato Z, et al. Clinical and radiological features of rotavirus cerebellitis. *American Journal of Neuroradiology* 2010;31(9):1591.
- [38] Mori T, Morii M, Kuroiwa Y, Hotsubo T, Fuse S, Tsustumi H. Rotavirus encephalitis and cerebellitis with reversible magnetic resonance signal changes. *Pediatrics international: official journal of the Japan Pediatric Society* 2011;53(2):252.

- [39] Lloyd MB, Lloyd JC, Gesteland PH, Bale Jr JF. Rotavirus Gastroenteritis and Seizures in Young Children. *Pediatric Neurology* 2010;42(6):404-408.
- [40] Obinata K, Okumura A, Nakazawa T, Kamata A, Niizuma T, Kinoshita K, et al. Norovirus Encephalopathy in a Previously Healthy Child. *The Pediatric infectious disease journal* 2010;29(11):1057-1059.
- [41] Kato Z, Manabe T, Teramoto T, Kondo N. Adenovirus infection mimics the cerebellitis caused by rotavirus infection. *European journal of pediatrics* 2011;170(3):1-2.
- [42] Grgic-Vitek M, Klavs I. High burden of tick-borne encephalitis in Slovenia-Challenge for vaccination policy. *Vaccine* 2011(May 26. [Epub ahead of print]).
- [43] Czupryna P, Moniuszko A, Pancewicz SA, Grygorczuk S, Kondrusik M, Zajkowska J. Tick-borne encephalitis in Poland in years 1993-2008--epidemiology and clinical presentation. A retrospective study of 687 patients. *Eur J Neurol* 2011;18(5):673-9.
- [44] Karelis G, Bormane A, Logina I, Lucenko I, Suna N, Krumina A, et al. Tick-borne encephalitis in Latvia 1973-2009: epidemiology, clinical features and sequelae. *Eur J Neurol* 2011.
- [45] Ehrlich HJ, Petermann R, Barrett PN. Re: Tick-borne encephalitis (TBE) trends in epidemiology and current and future management. *Travel Med Infect Dis* 2011;9(2):83.
- [46] Stefanoff P, Polkowska A, Giambi C, Levy-Bruhl D, O'Flanagan D, Dematte L, et al. Reliable surveillance of tick-borne encephalitis in European countries is necessary to improve the quality of vaccine recommendations. *Vaccine* 2011;29(6):1283-8.
- [47] Witt CJ, Richards AL, Masuoka PM, Foley DH, Buczak AL, Musila LA, et al. The AFHSC-Division of GEIS Operations Predictive Surveillance Program: a multidisciplinary approach for the early detection and response to disease outbreaks. *BMC Public Health* 2011;11 Suppl 2:S10.
- [48] Hossain MJ, Gurley ES, Montgomery S, Petersen L, Sejvar J, Fischer M, et al. Hospital-based surveillance for Japanese encephalitis at four sites in Bangladesh, 2003-2005. *Am J Trop Med Hyg* 2010;82(2):344-9.
- [49] Bista MB, Banerjee MK, Shin SH, Tandan JB, Kim MH, Sohn YM, et al. Efficacy of single-dose SA 14-14-2 vaccine against Japanese encephalitis: a case control study. *Lancet* 2001;358(9284):791.
- [50] Solomon T, Thao TT, Lewthwaite P, Ooi MH, Kneen R, Dung NM, et al. A cohort study to assess the new WHO Japanese encephalitis surveillance standards. *Bull World Health Organ* 2008;86(3):178-86.
- [51] Douglas A, Harris P, Francis F, Norton R. Herpes zoster meningoencephalitis: not only a disease of the immunocompromised? *Infection* 2010;38(1):73-5.
- [52] Braun-Falco M, Hoffmann M. Herpes zoster with progression to acute varicella zoster virus-meningoencephalitis. *Int J Dermatol* 2009;48(8):834-9.
- [53] Ziebold C, von Kries R, Lang R, Weigl J, Schmitt HJ. Severe complications of varicella in previously healthy children in Germany: a 1-year survey. *Pediatrics* 2001;108(5):E79.
- [54] Marchetto S, de Benedictis FM, de Martino M, Versace A, Chiappini E, Bertaine C, et al. Epidemiology of hospital admissions for chickenpox in children: an Italian multicentre study in the pre-vaccine era. *Acta Paediatr* 2007;96(10):1490-3.

- [55] Frenos S, Galli L, Chiappini E, de Martino M. An increasing incidence of chickenpox central nervous system complications in children: what's happening in Tuscany? *J Clin Virol* 2007;38(4):358-61.
- [56] Cameron JC, Allan G, Johnston F, Finn A, Heath PT, Booy R. Severe complications of chickenpox in hospitalised children in the UK and Ireland. *Arch Dis Child* 2007;92(12):1062-6.
- [57] Almuneef M, Memish ZA, Balkhy HH, Alotaibi B, Helmy M. Chickenpox complications in Saudi Arabia: Is it time for routine varicella vaccination? *Int J Infect Dis* 2006;10(2):156-61.
- [58] Azevedo RS, Amaku M. Modelling immunization strategies with cytomegalovirus vaccine candidates. *Epidemiol Infect* 2011;1-9.
- [59] Griffiths PD, Stanton A, McCarrell E, Smith C, Osman M, Harber M, et al. Cytomegalovirus glycoprotein-B vaccine with MF59 adjuvant in transplant recipients: a phase 2 randomised placebo-controlled trial. *Lancet* 2011;377(9773):1256-63.
- [60] Heineman TC. Human cytomegalovirus vaccines. 2007.
- [61] Sabbaj S, Pass RF, Goepfert PA, Pichon S. Glycoprotein B vaccine is capable of boosting both antibody and CD4 T-cell responses to cytomegalovirus in chronically infected women. *J Infect Dis* 2011;203(11):1534-41.
- [62] Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. *Rev Med Virol* 2007;17(5):355-63.
- [63] Berger A, Reitter A, Harter PN, Buxmann H, Allwinn R, Louwen F, et al. Problems and challenges in the diagnosis of vertical infection with human cytomegalovirus (CMV): Lessons from two accidental cases. *J Clin Virol* 2011.
- [64] Montesinos P, Sanz J, Cantero S, Lorenzo I, Martin G, Saavedra S, et al. Incidence, risk factors, and outcome of cytomegalovirus infection and disease in patients receiving prophylaxis with oral valganciclovir or intravenous ganciclovir after umbilical cord blood transplantation. *Biol Blood Marrow Transplant* 2009;15(6):730-40.
- [65] Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. *Rev Med Virol* 2007;17(4):253-76.
- [66] Miron D, Brosilow S, Felszer K, Reich D, Halle D, Wachtel D, et al. Incidence and clinical manifestations of breast milk-acquired Cytomegalovirus infection in low birth weight infants. *J Perinatol* 2005;25(5):299-303.
- [67] Amin R, Ford-Jones E, Richardson SE, MacGregor D, Tellier R, Heurter H, et al. Acute childhood encephalitis and encephalopathy associated with influenza: a prospective 11-year review. *Pediatr Infect Dis J* 2008;27(5):390-5.
- [68] Maricich SM, Neul JL, Lotze TE, Cazacu AC, Uyeki TM, Demmler GJ, et al. Neurologic complications associated with influenza A in children during the 2003-2004 influenza season in Houston, Texas. *Pediatrics* 2004;114(5):e626-33.
- [69] Okabe N, Yamashita K, Taniguchi K, Inouye S. Influenza surveillance system of Japan and acute encephalitis and encephalopathy in the influenza season. *Pediatr Int* 2000;42(2):187-91.

- [70] Ono S, Kudo M, Aoki K, Ezaki F, Misumi J. Effect of mass immunization against influenza encephalopathy on mortality rates in children. *Pediatr Int* 2003;45(6):680-7.
- [71] Steininger C, Popow-Kraupp T, Laferl H, Seiser A, Godl I, Djamshidian S, et al. Acute encephalopathy associated with influenza A virus infection. *Clin Infect Dis* 2003;36(5):567-74.
- [72] Togashi T, Matsuzono Y, Narita M. Epidemiology of influenza-associated encephalitis-encephalopathy in Hokkaido, the northernmost island of Japan. *Pediatr Int* 2000;42(2):192-6.
- [73] Togashi T, Matsuzono Y, Narita M, Morishima T. Influenza-associated acute encephalopathy in Japanese children in 1994-2002. *Virus Res* 2004;103(1-2):75-8.
- [74] Wada T, Morishima T, Okumura A, Tashiro M, Hosoya M, Shiomi M, et al. Differences in clinical manifestations of influenza-associated encephalopathy by age. *Microbiol Immunol* 2009;53(2):83-8.
- [75] Yoshikawa H, Yamazaki S, Watanabe T, Abe T. Study of influenza-associated encephalitis/encephalopathy in children during the 1997 to 2001 influenza seasons. *J Child Neurol* 2001;16(12):885-90.
- [76] Citerio G, Sala F, Patruno A, Gori A, Grioni D, Rossi M, et al. Influenza A (H1N1) encephalitis with severe intracranial hypertension. *Minerva Anestesiol*;76(6):459-62.
- [77] Fluss J, Ferey S, Menache-Starobinski C, Delavelle J, Van Bogaert P, Vargas MI. Mild influenza-associated encephalopathy/encephalitis with a reversible splenic lesion in a Caucasian child with additional cerebellar features. *Eur J Paediatr Neurol*;14(1):97-100.
- [78] Gika AD, Rich P, Gupta S, Neilson DE, Clarke A. Recurrent acute necrotizing encephalopathy following influenza A in a genetically predisposed family. *Dev Med Child Neurol*;52(1):99-102.
- [79] Goenka AH, Mukund A, Ahuja J, Kumar A. Reversible lesion in the splenium of the corpus callosum in a child with influenza-associated encephalitis-encephalopathy (IAEE). *J Clin Neurosci*;17(5):607, 678.
- [80] Ichiyama T. Acute encephalopathy/encephalitis in childhood: a relatively common and potentially devastating clinical syndrome. *Brain Dev*;32(6):433-4.
- [81] Kulkarni R, Kinikar A. Encephalitis in a child with H1N1 infection: First case report from India. *J Pediatr Neurosci*;5(2):157-9.
- [82] Landau YE, Grisaru-Soen G, Reif S, Fattal-Valevski A. Pediatric Neurologic Complications Associated With Influenza A H1N1. *Pediatr Neurol*;44(1):47-51.
- [83] Lyon JB, Remigio C, Milligan T, Deline C. Acute necrotizing encephalopathy in a child with H1N1 influenza infection. *Pediatr Radiol*;40(2):200-5.
- [84] Martin A, Reade EP. Acute necrotizing encephalopathy progressing to brain death in a pediatric patient with novel influenza A (H1N1) infection. *Clin Infect Dis*;50(8):e50-2.
- [85] Ormitti F, Ventura E, Summa A, Picetti E, Crisi G. Acute necrotizing encephalopathy in a child during the 2009 influenza A(H1N1) pandemic: MR imaging in diagnosis and follow-up. *AJNR Am J Neuroradiol*;31(3):396-400.
- [86] Rellosa N, Bloch KC, Shane AL, Debiase RL. Neurologic manifestations of pediatric novel h1n1 influenza infection. *Pediatr Infect Dis J*;30(2):165-7.

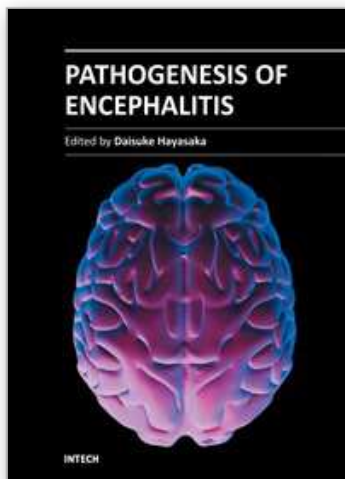
- [87] Samuel N, Attias O, Tatour S, Brik R. Novel influenza A (H1N1) and acute encephalitis in a child. *Isr Med Assoc J*;12(7):446-7.
- [88] Webster RI, Hazelton B, Suleiman J, Macartney K, Kesson A, Dale RC. Severe encephalopathy with swine origin influenza A H1N1 infection in childhood: case reports. *Neurology*;74(13):1077-8.
- [89] Sejvar JJ, Kohl KS, Bilynsky R, Blumberg D, Cvetkovich T, Galama J, et al. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine* 2007;25(31):5771-92.
- [90] Ward KN, Bryant NJ, Andrews NJ, Bowley JS, Ohrling A, Verity CM, et al. Risk of serious neurologic disease after immunization of young children in Britain and Ireland. *Pediatrics* 2007;120(2):314-21.
- [91] Okais C, Gay C, Seon F, Buchaille L, Chary E, Soubeyrand B. Disease-specific adverse events following nonlive vaccines: A paradoxical placebo effect or a nocebo phenomenon? *Vaccine* 2011;May 31. [Epub ahead of print].
- [92] Bonhoeffer J, Menkes J, Gold MS, de Souza-Brito G, Fisher MC, Halsey N, et al. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. *Vaccine* 2004;22(5-6):557-62.
- [93] Rath B, Magnus M, Heininger U. Evaluating the Brighton Collaboration case definitions, aseptic meningitis, encephalitis, myelitis, and acute disseminated encephalomyelitis, by systematic analysis of 255 clinical cases. *Vaccine* 2010;28(19):3488-95.
- [94] Devrim I, Tezer H, Haliloglu G, Kara A, Secmeer G. Relapsing Herpes simplex virus encephalitis despite high-dose acyclovir therapy: a case report. *Turk J Pediatr* 2008;50(4):380-2.
- [95] Jha S, Patel R, Yadav RK, Kumar V. Clinical spectrum, pitfalls in diagnosis and therapeutic implications in herpes simplex encephalitis. *J Assoc Physicians India* 2004;52:24-6.
- [96] James SH, Whitley RJ. Treatment of herpes simplex virus infections in pediatric patients: current status and future needs. *Clin Pharmacol Ther* 2010;88(5):720-4.
- [97] Jones CA, Walker KS, Badawi N. Antiviral agents for treatment of herpes simplex virus infection in neonates. *Cochrane Database Syst Rev* 2009(3):CD004206.
- [98] Long SS, Pool TE, Vodzak J, Daskalaki I, Gould JM. Herpes simplex virus infection in young infants during 2 decades of empiric acyclovir therapy. *Pediatr Infect Dis J* 2011;30(7):556-61.
- [99] Wang IJ, Lee PI, Huang LM, Chen CJ, Chen CL, Lee WT. The correlation between neurological evaluations and neurological outcome in acute encephalitis: a hospital-based study. *Eur J Paediatr Neurol* 2007;11(2):63-9.
- [100] Tamma PD, Agwu AL, Hartman AL. Behavior Outbursts, Orofacial Dyskinesias, and CSF Pleocytosis in a Healthy Child. *Pediatrics* 2011;Jun 6. [Epub ahead of print].
- [101] Banatvala JE. Herpes simplex encephalitis. *Lancet Infect Dis* 2011;11(2):80-1.

- [102] Huang MC, Wang SM, Hsu YW, Lin HC, Chi CY, Liu CC. Long-term cognitive and motor deficits after enterovirus 71 brainstem encephalitis in children. *Pediatrics* 2006;118(6):e1785.
- [103] Schessl J, Luther B, Kirschner J, Mauff G, Korinthenberg R. Infections and vaccinations preceding childhood Guillain-Barre syndrome: a prospective study. *Eur J Pediatr* 2006;165(9):605-12.
- [104] Huang MC, Wang SM, Hsu YW, Lin HC, Chi CY, Liu CC. Long-term cognitive and motor deficits after enterovirus 71 brainstem encephalitis in children. *Pediatrics* 2006;118(6):e1785-8.
- [105] Diedrich S, Claus H, Schreier E. Immunity status against poliomyelitis in Germany: determination of cut-off values in International Units. *BMC Infect Dis* 2002;2:2.
- [106] Diedrich S, Schreier E. Aseptic meningitis in Germany associated with echovirus type 13. *BMC Infect Dis* 2001;1:14.
- [107] Mailles A, Stahl JP. Infectious encephalitis in France in 2007: a national prospective study. *Clin Infect Dis* 2009;49(12):1838-47.
- [108] Lee TC, Tsai CP, Yuan CL, Wei CY, Tsao WL, Lee RJ, et al. Encephalitis in Taiwan: a prospective hospital-based study. *Jpn J Infect Dis* 2003;56(5-6):193-9.
- [109] Ilias A, Galanakis E, Raissaki M, Kalmanti M. Childhood encephalitis in Crete, Greece. *J Child Neurol* 2006;21(10):910-2.
- [110] Beig FK, Malik A, Rizvi M, Acharya D, Khare S. Etiology and clinico-epidemiological profile of acute viral encephalitis in children of western Uttar Pradesh, India. *Int J Infect Dis* 2010;14(2):e141-6.
- [111] Anga G, Barnabas R, Kaminien O, Tefuarani N, Vince J, Ripa P, et al. The aetiology, clinical presentations and outcome of febrile encephalopathy in children in Papua New Guinea. *Ann Trop Paediatr* 2010;30(2):109-18.
- [112] Elbers JM, Bitnun A, Richardson SE, Ford-Jones EL, Tellier R, Wald RM, et al. A 12-year prospective study of childhood herpes simplex encephalitis: is there a broader spectrum of disease? *Pediatrics* 2007;119(2):e399.
- [113] Glaser CA, Gilliam S, Schnurr D, Forghani B, Honarmand S, Khetsuriani N, et al. In search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project, 1998-2000. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 2003;36(6):731.
- [114] Morishima T, Togashi T, Yokota S, Okuno Y, Miyazaki C, Tashiro M, et al. Encephalitis and encephalopathy associated with an influenza epidemic in Japan. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 2002;35(5):512.
- [115] Olsen SJ, Supawat K, Campbell AP, Anantapreecha S, Liamsuwan S, Tunlayadechanont S, et al. Japanese encephalitis virus remains an important cause of encephalitis in Thailand. *Int J Infect Dis* 2010;14(10):e888-92.
- [116] Schubart CD, Mturi N, Beld MG, Wertheim PM, Newton CR. Role of viruses in Kenyan children presenting with acute encephalopathy in a malaria-endemic area. *Am J Trop Med Hyg* 2006;75(6):1148-50.

- [117] Kolski H, Ford-Jones EL, Richardson S, Petric M, Nelson S, Jamieson F, et al. Etiology of acute childhood encephalitis at The Hospital for Sick Children, Toronto, 1994-1995. *Clin Infect Dis* 1998;26(2):398-409.

IntechOpen

IntechOpen



Pathogenesis of Encephalitis

Edited by Dr. Daisuke Hayasaka

ISBN 978-953-307-741-3

Hard cover, 344 pages

Publisher InTech

Published online 09, December, 2011

Published in print edition December, 2011

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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Barbara Rath (2011). The Value of Standardized Case Definitions in Encephalitis Clinical Research, Pathogenesis of Encephalitis, Dr. Daisuke Hayasaka (Ed.), ISBN: 978-953-307-741-3, InTech, Available from: <http://www.intechopen.com/books/pathogenesis-of-encephalitis/the-value-of-standardized-case-definitions-in-encephalitis-clinical-research>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen