Recent updates and emerging challenges in children with encephalitis

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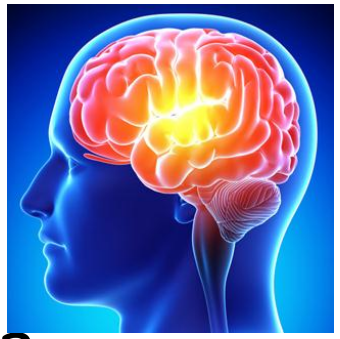
Overview of the talk

- Encephalitis
- Epidemiology
- Etiology
- Clinical presentation (infectious/autoimmune)
- Diagnosis
- Management
- Challenges

What is Encephalitis ?



- Inflammation of the brain parenchyma, manifest by neurologic dysfunction, such as:
  - altered mental status, behavior, or personality changes
  - motor or sensory deficits
  - speech or movement disorders
  - seizure

Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 7th ed, 2014. p.492.

Epidemiology

- Exact incidence is not known
- 3.2-10.5 per 100,000 hospitalizations
- Globally, an estimated 390 million people are affected by infectious encephalitis annually

Etiology

- Two main groups
  - Infectious encephalitis
  - Immune mediated encephalitis

- Majority – unknown etiology
- Of known etiology, viruses are commonest cause among infectious encephalitis
- Identifiable etiology in <50% in most studies

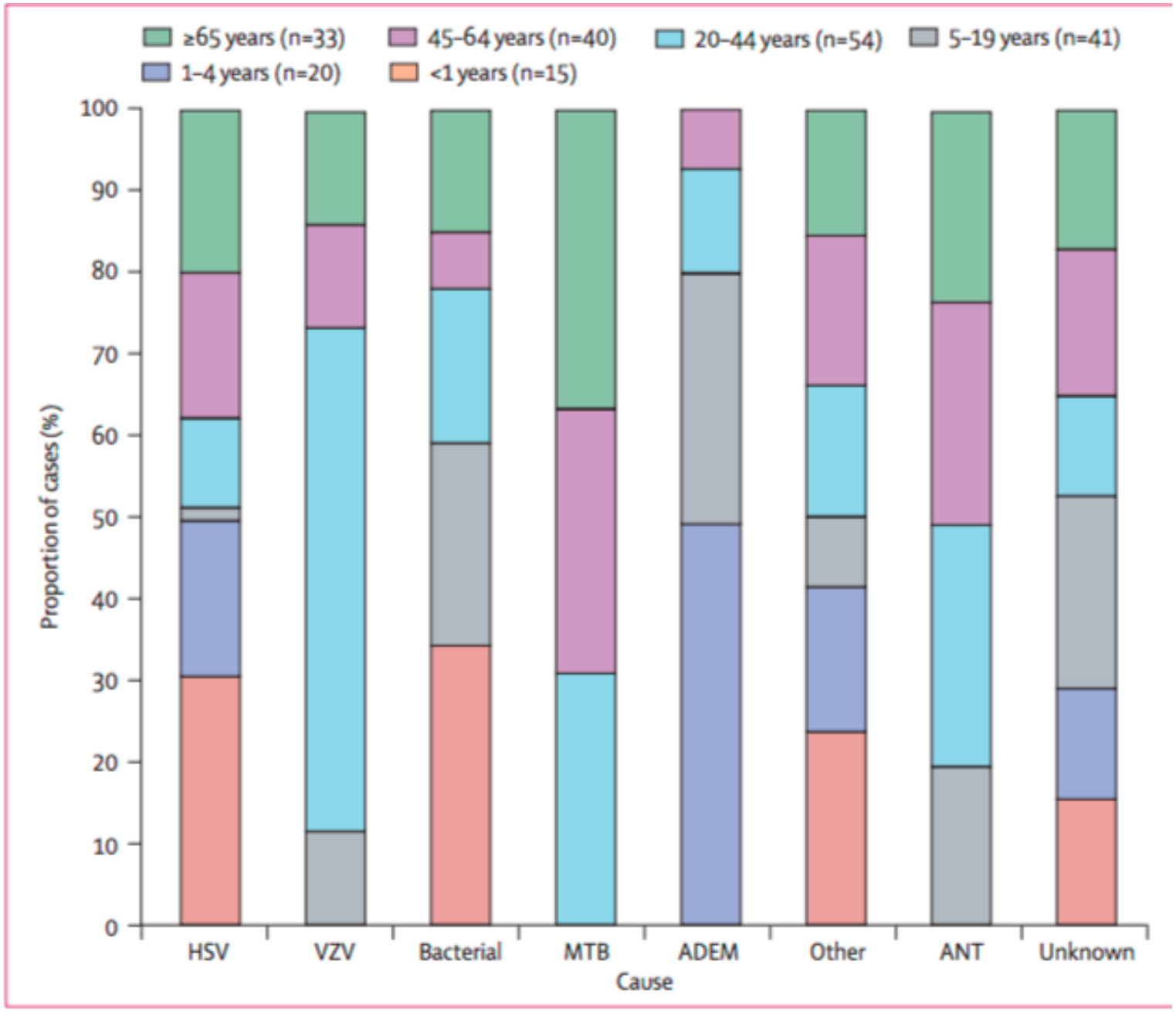
Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study

Julia Granerod, Helen E Ambrose, Nicholas W S Davies, Jonathan P Clewley, Amanda L Walsh, Dilys Morgan, Richard Cunningham, Mark Zuckerman, Ken J Mutton, Tom Solomon, Katherine N Ward, Michael P T Lunn, Sarosh R Irani, Angela Vincent, David W G Brown, Natasha S Crowcroft, on behalf of the UK Health Protection Agency (HPA) Aetiology of Encephalitis Study Group

Summary

Background Encephalitis has many causes, but for most patients the cause is unknown. We aimed to establish the cause and identify the clinical differences between causes in patients with encephalitis in England.

Methods Patients of all ages and with symptoms suggestive of encephalitis were actively recruited for 2 years (staged start between October, 2005, and November, 2006) from 24 hospitals by clinical staff. Systematic laboratory testing included PCR and antibody assays for all commonly recognised causes of infectious encephalitis, investigation for less commonly recognised causes in immunocompromised patients, and testing for travel-related causes if indicated. We also tested for non-infectious causes for acute encephalitis including autoimmunity. A multidisciplinary expert team reviewed clinical presentation and hospital tests and directed further investigations. Patients were followed up for 6 months after discharge from hospital.


≥65 years (n=33)
45–64 years (n=40)
20–44 years (n=54)
5–19 years (n=41)
1–4 years (n=20)
<1 years (n=15)
Proportion of cases (%)
100
90
80
70
60
50
40
30
20
10
0
HSV
VZV
Bacterial
MTB
ADEM
Other
ANT
Unknown
Cause

	Confirmed	Probable	Total (%)
Infectious cause (n=86 [42%; 95% CI 35–49%])			
Herpes simplex virus	36	2	38* (19)
Mycobacterium tuberculosis	1	9	10 (5)
Varicella zoster virus	9	1	10 (5)
Streptococci	2	2	4† (2)
Enteroviruses	3	–	3 (1)
Dual infection	3	–	3‡ (1)
Streptococcus pneumoniae	3	–	3 (1)
Influenza A	–	2	2 (1)
Neisseria meningitidis	2	–	2 (1)
Toxoplasma gondii	2	–	2 (1)
Coxiella burnetii	–	1	1 (0·5)
Epstein-Barr virus	–	1	1 (0·5)
Enterococcus faecium	1	–	1 (0·5)
Human herpesvirus-6	–	1	1 (0·5)
HIV	1	–	1 (0·5)
JC virus	1	–	1 (0·5)
Listeria monocytogenes	1	–	1 (0·5)
Pseudomonas spp	1	–	1 (0·5)
Sclerosing subacute panencephalitis (measles)	1	–	1 (0·5)
Immune-mediated cause (n=42 [21%; 95% CI 15–27%])			
Acute disseminated encephalomyelitis	23	–	23 (11)
NMDA receptor antibodies	9	–	9 (4)
VGKC antibodies	7	–	7 (3)
Secondary to systemic vasculitis	1	–	1 (0·5)
Multiple sclerosis	1	–	1 (0·5)
Paraneoplastic	1	–	1 (0·5)
Unknown cause (n=75 [37%; 95% CI 30–44%])			
Unknown	–	–	75 (37)
Total			203

	Immunocompetent patients* (n=172)	Immunocompromised patients† (n=31)	Total
Herpes simplex virus	37 (22%, 16–28)	1 (3%, 0·1–17)	38
Acute disseminated encephalomyelitis	23 (14%, 9–19)	..	23
Antibody-associated encephalitis	15 (9%, 5–14)	1 (3%, 0·1–17)	16
Mycobacterium tuberculosis	9 (5%, 2–10)	1 (3%, 0·1–17)	10
Varicella zoster virus	4 (2%, 0·6–6)	6 (19%, 7–37)	10
Streptococci	4 (2%, 0·6–6)	..	4
Enterovirus	3 (2%, 0·4–5)	..	3
Dual finding	..	3 (10%, 2–26)	3
Toxoplasma gondii	..	2 (6%, 1–21)	2
Epstein-Barr virus	..	1 (3%, 0·1–17)	1
Human herpesvirus-6	..	1 (3%, 0·1–17)	1
HIV	..	1 (3%, 0·1–17)	1
JC virus	..	1 (3%, 0·1–17)	1
Listeria monocytogenes	..	1 (3%, 0·1–17)	1
Pneumococcus	..	1 (3%, 0·1–17)	1
Other‡	13 (8%, 4–13)	..	13
Unknown	64 (37%, 30–45)	11 (35%, 19–55)	75

Data are number (%, 95% CI). The dual findings are the same as for table 2. *Includes cases for whom immune status was unknown. †Reasons for immunocompromised status: 18 HIV positive; three on chemotherapy; ten with other reasons or exact reason unknown. ‡Other causes include *Pseudomonas* spp, *Coxiella burnetii*, *Enterococcus faecium*, meningococcus, pneumococcus, influenza A, sclerosing subacute panencephalitis, paraneoplastic encephalitis, multiple sclerosis, and encephalitis secondary to systemic vasculitis.

Table 2: **Causes of encephalitis in immunocompetent versus immunocompromised patients**

Ai *et al. BMC Infectious Diseases* (2017) 17:494
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BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Etiology and prognosis of acute viral encephalitis and meningitis in Chinese children: a multicentre prospective study

Junhong Ai[1], Zhengde Xie[1*], Gang Liu[1], Zongbo Chen[2], Yong Yang[3], Yuning Li[4], Jing Chen[5], Guo Zheng[5] and Kunling Shen[6*]

Multicenter study in China

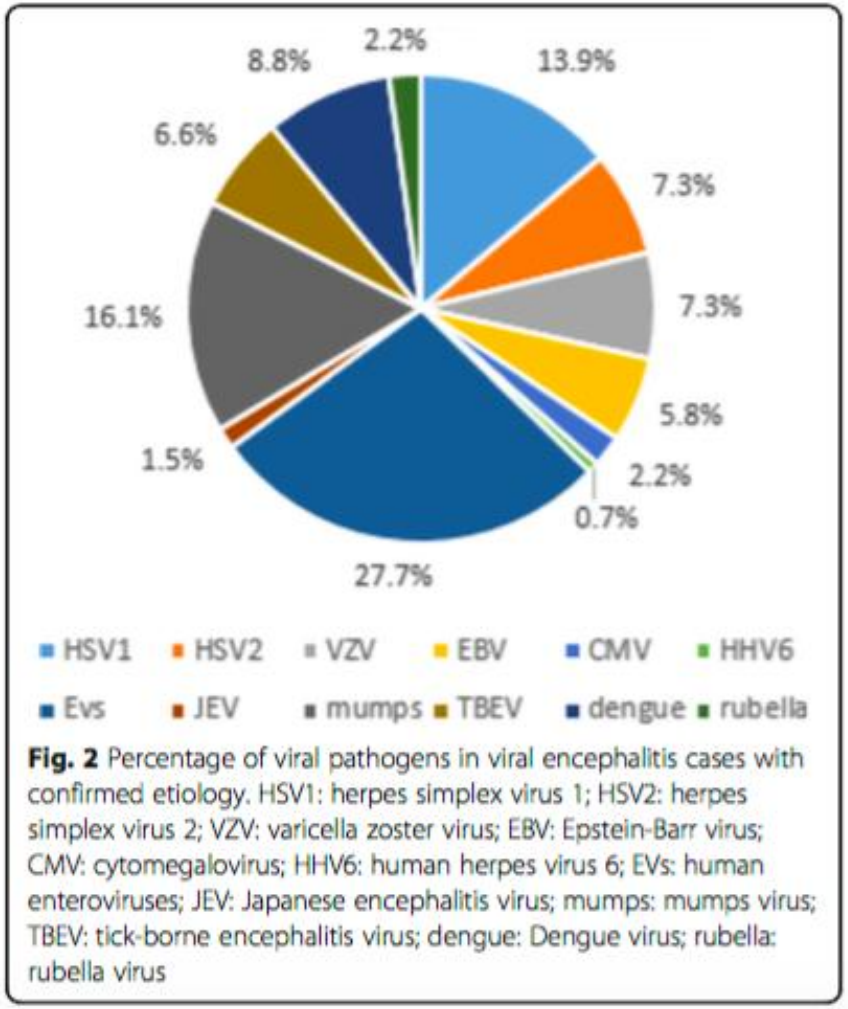


Fig. 2 Percentage of viral pathogens in viral encephalitis cases with confirmed etiology. HSV1: herpes simplex virus 1; HSV2: herpes simplex virus 2; VZV: varicella zoster virus; EBV: Epstein-Barr virus; CMV: cytomegalovirus; HHV6: human herpes virus 6; EVs: human enteroviruses; JEV: Japanese encephalitis virus; mumps: mumps virus; TBEV: tick-borne encephalitis virus; dengue: Dengue virus; rubella: rubella virus

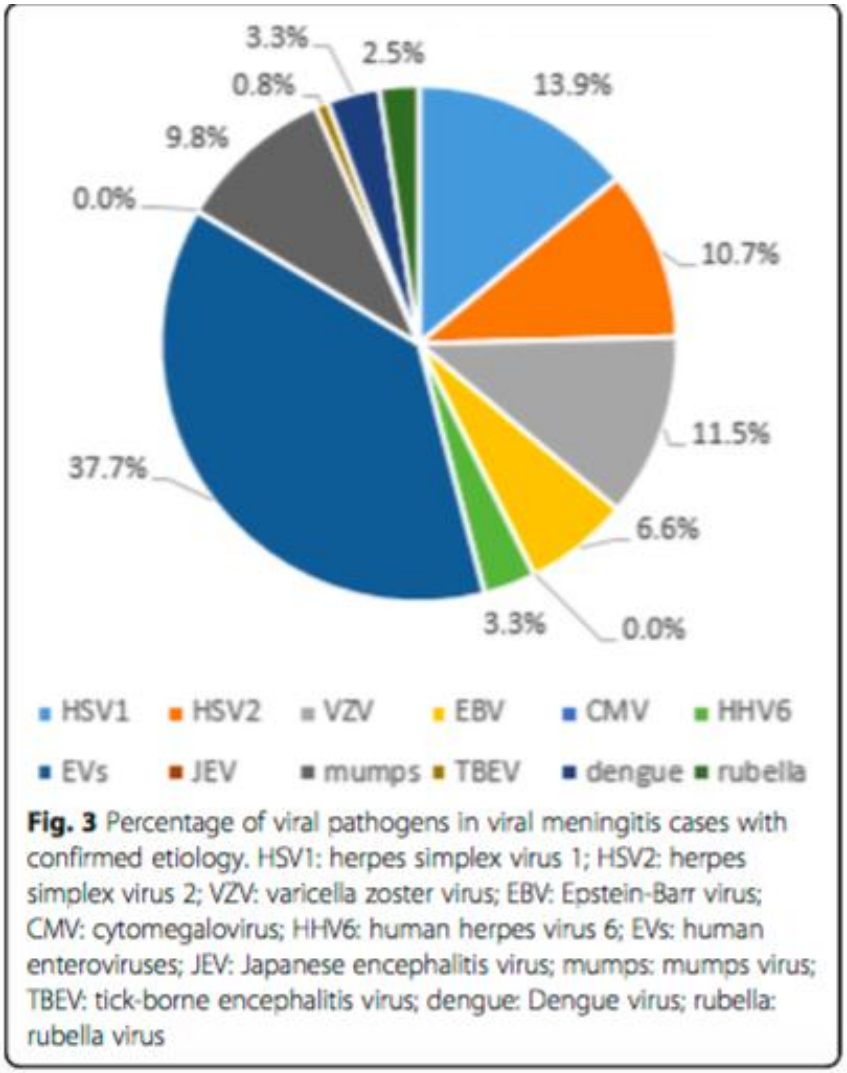


Fig. 3 Percentage of viral pathogens in viral meningitis cases with confirmed etiology. HSV1: herpes simplex virus 1; HSV2: herpes simplex virus 2; VZV: varicella zoster virus; EBV: Epstein-Barr virus; CMV: cytomegalovirus; HHV6: human herpes virus 6; EVs: human enteroviruses; JEV: Japanese encephalitis virus; mumps: mumps virus; TBEV: tick-borne encephalitis virus; dengue: Dengue virus; rubella: rubella virus

- HSV – commonest in USA, England, France, Italy, Australia, Eastern India
- Human enteroviruses in China, Greece, India
- JE in Vietnam

Infectious encephalitis

- Mainly viruses
- Bacteria
- Parasites
- fungus
- Different etiological agents in different geographical regions

Clinical presentation of IE

- Acute encephalitis syndrome (AES)
- Many cases of encephalitis are ‘non-specific’ OR “unknown causes”
- Diagnostic facilities are limited in resource poor setting
- Initial presentation can be due to other causes like bacteria/TB/malaria

WHO case definition

- 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

Clinical manifestations

- Depends on which part of CNS affected
- Pathogenic agent
- Various host factors
- Non-specific sign and symptoms in neonates and young infants
- Fever may not be present

Autoimmune encephalitis

Pathophysiology

- Antibodies against neuronal proteins
- Cell surface proteins vs intracellular proteins

Intracellular antigens

Antigen	Neurological symptoms	Others
Hu (ANNA1)	Encephalomyelitis, PCD, Brainstem encephalitis, focal cortical encephalitis, limbic encephalitis	Mostly adults and associated with cancer
CRMP5	Encephalomyelitis, chorea, limbic encephalitis	
Amphiphysin	Stiff-person syndrome, myelopathy and myoclonus, encephalomyelitis	
Ri (ANNA 2)	Brainstem encephalitis, opsoclonus myoclonus	
Ma2	Diencephalitic, limbic encephalitis, brainstem encephalitis	
GAD 65	Ataxia, stiff person syndrome, epilepsy	Adults, <10% associated with tumor

Cell surface antigens

Antigen	Neurological symptoms	Others
NMDAR receptor (NR1 subunit)	Behavioural disturbance, psychosis, catatonia, seizures, aphasia, movement disorders including orolingual dyskinesias, central hypoventilation, dysautonomia	Children 40%, medial temporal lobe hyperintensity 80% respond to immunotherapy, 12-25% relapse rate
CASPR2	Morvan's syndrome, encephalitis, peripheral nerve hyperexcitability	Adults Thymoma in 20-40%
Glycine R	Progressive encephalomyelitis with rigidity, stiff person syndrome	Adults, associated with thymoma, Hodgkin's lymphoma

Antigen	Neurological symptoms	Others
GABAAR	Refractory seizures, status epilepticus, stiff person syndrome, OMS	No clear cancer association,
GABABR (B1 subunit)	Classic limbic encephalitis. Early and prominent seizures	Adults, lung cancer
AMPAR (Glu R1/2 subunit)	Limbic encephalitis, psychosis	Adults, 70% tumor (lung, breast)
LGI1	Faciobrachial dystonic seizures, limbic encephalitis, epilepsy (often tonic seizures), myoclonus, rapidly progressive dementia (can mimic CJD), sleep disorders	Mainly adults <20% associated with tumor

antiNMDAR encephalitis

- Neuropsychiatric symptoms
  - behavior problems
  - change in personality
  - depression, anxiety, fear, psychosis, hallucinations
  - ADHD, OCD

Neurological symptoms

- Memory loss or amnesia
- movement disorders & dystonia
- Seizures
- aphasia, mutism
- sleep disorders
- decreased level of consciousness
- autonomic features: instability of body temperature, hypoventilation, respiratory failure

Movement disorders

- video

- video

Case 1

- Previously well 10 yr old girl
- Presented with decline in school performance
- Abnormal behavior
- Irrelevant talk
- Poor sleep
- No seizure
- Came to YCH 6 months after symptoms onset

- video

- CSF RE normal
- MRI brain normal
- NMDAR ab positive in both serum and CSF
- No tumor on USG
- Treated with methylprednisolone followed by IVIg
- Complete recovery after IVIg

Relapsed after 1 year

- video

After treatment

- video

Case 2

- 6 yr old boy
- Post encephalitis sequale
- Admitted for increasing dystonia and refractory seizures
- He had aphasia, movement disorders, sleep disorders, seizures, hypersalivation

Movement disorders

- video

- NMDAR ab was positive in both serum and CSF
- Treated with IV methylprednisolone
- No significant improvement after 2 weeks
- Started IVIg 2g/kg
- Significant improvement after 2 weeks

Follow up

- video

Case 3

- 6yr old boy
- Previously normal
- HSE 6 weeks ago
- Admitted with
  - memory loss
  - Aphasia
  - Poor sleep
  - Behavior ptoblem

- Conscious but unable to talk
- No weakness or neurological deficit
- Orofacial dyskinesia
- Hypersalivation

Orofacial dyskinesia andhypersalivation

- video

- video

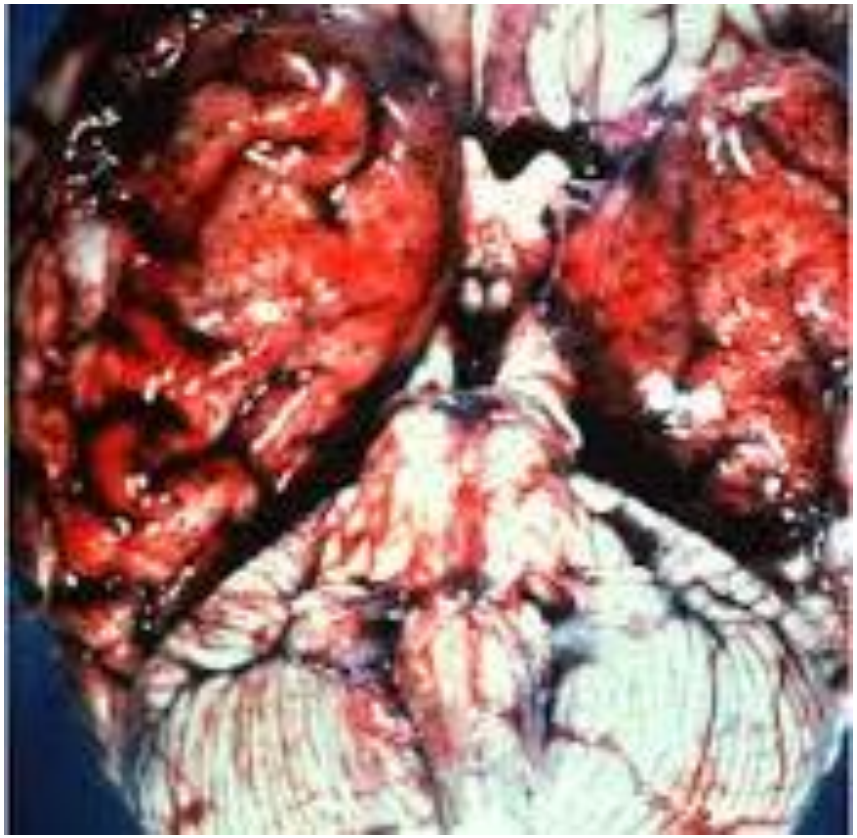
- video

- video

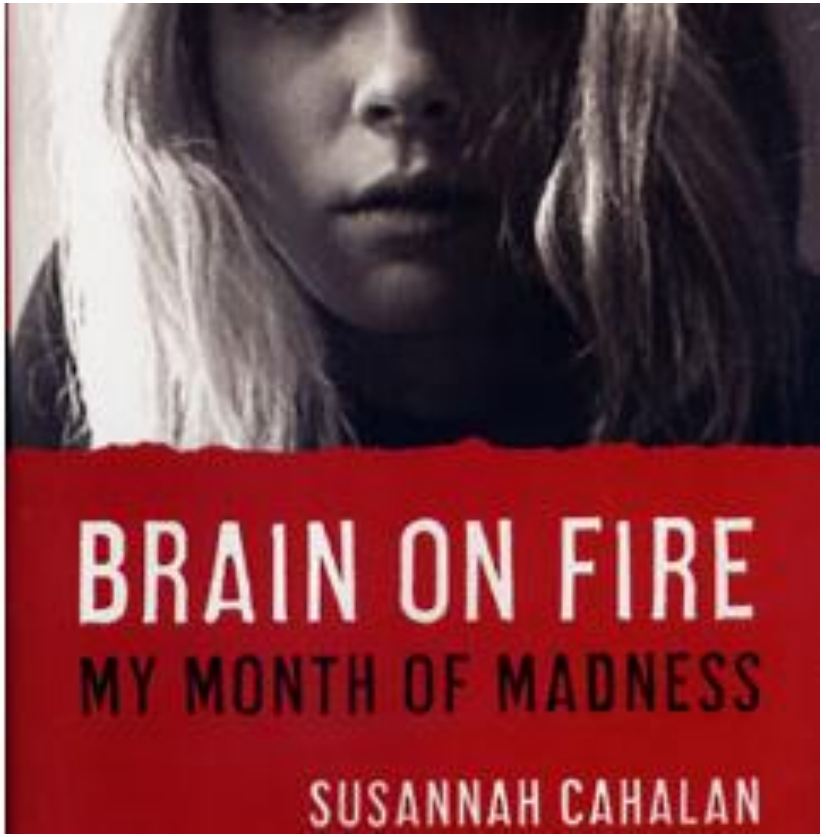
Encephalitis

Infection or immune?

HSE



NMDAR encephalitis



2012

N-Methyl-$_D$-Aspartate Receptor Antibodies in Herpes Simplex Encephalitis

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2014

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Herpes Simplex Virus Encephalitis is a Trigger of Brain Autoimmunity

Thaís Armangue, M.D.[1,2,*], **Frank Leypoldt, M.D., PhD.**[1,3,*], **Ignacio Málaga, M.D., PhD.**[4], **Miquel Raspall-Chaure, M.D.**[2], **Itxaso Marti, M.D.**[5], **Charles Nichter, M.D.**[6], **John Pugh, M.D.**[6], **Monica Vicente-Rasoamalala, M.D.**[7], **Miguel Lafuente-Hidalgo, M.D.**[5], **Alfons Macaya, M.D., PhD.**[2], **Michael Ke, M.D., Ph.D.**[8], **Maarten J Titulaer, M.D., PhD.**[9], **Romana Höftberger, M.D.**[1,10], **Heather Sheriff**[11], **Carol Glaser, M.D., Ph.D.**[11], and **Josep Dalmau, M.D., Ph.D.**[1,12,13]

2014

Research

Case Report/Case Series

Herpes Simplex Encephalitis as a Potential Cause of Anti-*N*-Methyl-D-Aspartate Receptor Antibody Encephalitis Report of 2 Cases

Allen DeSena, MD, MPH; Donna Graves, MD; Worthy Warnack, MD; Benjamin M. Greenberg, MD, MHS

IMPORTANCE Encephalitis mediated by anti-*N*-methyl-D-aspartate (NMDA) receptor antibodies and herpes simplex (HS) encephalitis are seemingly separate causes of encephalopathy in adults and children. Herpes simplex encephalitis is infectious, and anti-NMDA receptor antibody encephalitis is autoimmune in origin. Both can cause seizures and encephalopathy, although the latter can also cause psychiatric symptoms and movement

Author Audio Interview at jamaneurology.com

Diagnosis

- High index of suspicion
- In any case of encephalitis clinically not suggestive of infectious encephalitis, and after exclusion of other possible causes

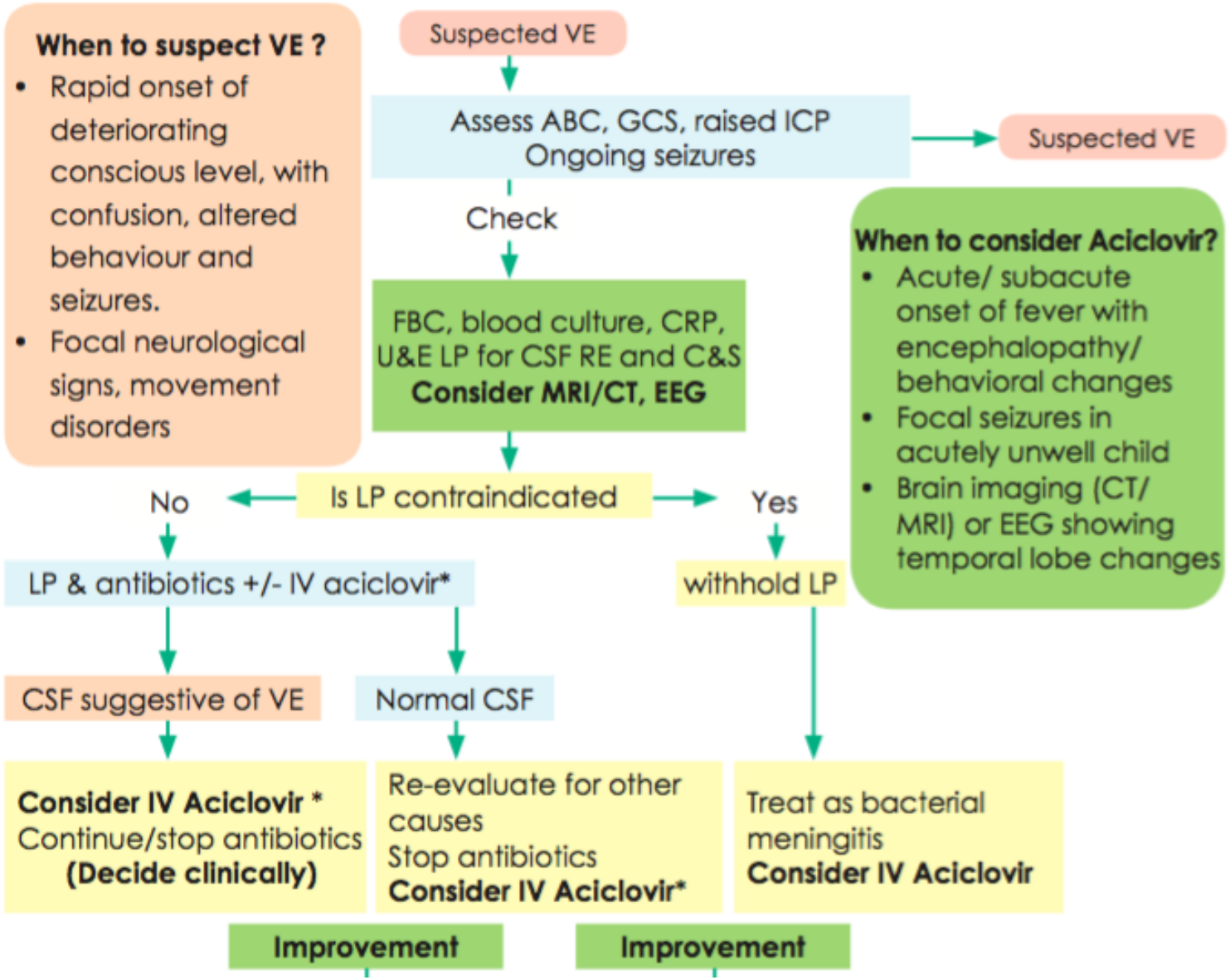
Diagnostic criteria for possible autoimmune encephalitis

Diagnosis can be made when all three of the following criteria have been met:

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms
2. At least one of the following:
    1. New focal CNS findings
    2. Seizures not explained by a previously known seizure disorder
    3. CSF pleocytosis (white blood cell count of more than five cells per mm^3)
    4. MRI features suggestive of encephalitis
3. Reasonable exclusion of alternative causes

Management of encephalitis

Approach to Children with Suspected Viral Encephalitis (VE)



Improvement

Complete course of IVAciclovir
(IV 3 weeks)

Improvement

Ongoing seizures?
Re-consider bacterial meningitis
Consider TB/Fungal
Consider Immune Encephalitis

Note

- If the initial CT/MRI and EEG do not indicate a focal area of abnormality, consider repeating them after 7 days of treatment. If there are still no focal areas of abnormality, and the CSF is normal and HSV PCR is negative, then stop treatment with Aciclovir
- The PCR for HSV can be supportive of the diagnosis, but a negative result should not be taken to mean the child does not have HSV encephalitis
- Treat if in doubt and there is no alternative diagnosis

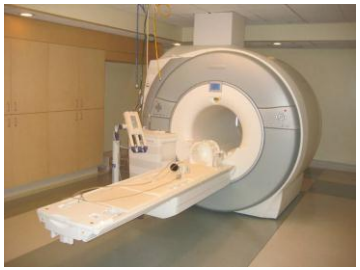
When to consider Immune Encephalitis?

- If the onset is subacute/biphasic
- If there are seizures, altered mental status or psychiatric symptoms, movement disorders, speech/sleep dysfunction, autonomic features, or short-term memory loss
- After exclusion of alternative causes including infectious causes of encephalitis

Challenges

Challenges in diagnosis

- Meningitis?
- Encephalitis?
- Meningoencephalitis?
- Autoimmune encephalitis?
- Limited resources – lab/imaging



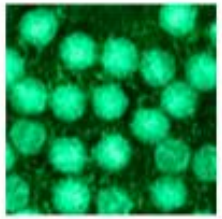
New technology

- Filmarray PCR
- 4 panels (resp, GI, ME, blood culture)
- Result available within 1 h

1 Test. 15 Targets. All in about an hour.

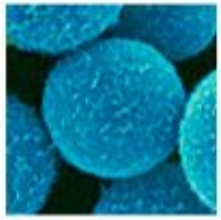
Bacteria

Escherichia coli K1
Haemophilus influenzae
Listeria monocytogenes
Neisseria meningitidis
Streptococcus agalactiae
Streptococcus pneumoniae



Viruses

Cytomegalovirus (CMV)
Enterovirus
Epstein-Barr virus (EBV)
Herpes simplex virus 1 (HSV-1)
Herpes simplex virus 2 (HSV-2)
Human herpesvirus 6 (HHV-6)
Human parechovirus
Varicella zoster virus (VZV)

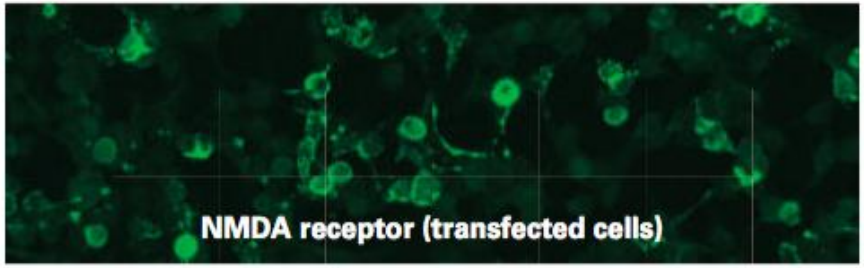


Yeast

Cryptococcus neoformans/gattii

Test for NMDAR Ab

Anti-Glutamate Receptor (Type NMDA) IIFT



- BIOCHIP Mosaic for sensitive detection of antibodies against glutamate receptors (type NMDAR) in anti-NMDA receptor encephalitis
- Highly specific and sensitive determination of antibodies in serum or CSF using recombinant cell lines

Challenges in management

- No specific antimicrobial therapy for most cases of viral encephalitis
- IV aciclovir is expensive
- Many patients seek medical advice at late stage
- Prolong ICU stay
- Neurological sequale are slow to recover

- Autoimmune encephalitis can be mistaken as psychiatric disorder
- Many symptoms overlap with infectious encephalitis and other neurological conditions
- IVIg is expensive
- Long term prospective cohort studies needed to understand more about AE

Thank you