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Herpes Simplex Virus Encephalitis: pitfalls in diagnosis, treatment and role in autoimmune encephalitis

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Conflicts of interest

Research sponsered by

- Netherlands Organisation for Scientific Research
- Stichting de Merel
- Amsterdam Neuroscience

No conflicts of interest

"Try this—I just bought a hundred shares."

A call from Spain

20 year-old Dutch woman

Studying in University in Spain

Fever, headache and confusion

Progression to coma

Suspected Herpes encephalitis, start aciclovir

1st CSF negative for HSV, 15 leukocytes/mm^3

A call from Spain

Questions Father

- are we sure it is encephalitis?

- is it herpes simplex virus encephalitis?

Encephalitis

Major health problem

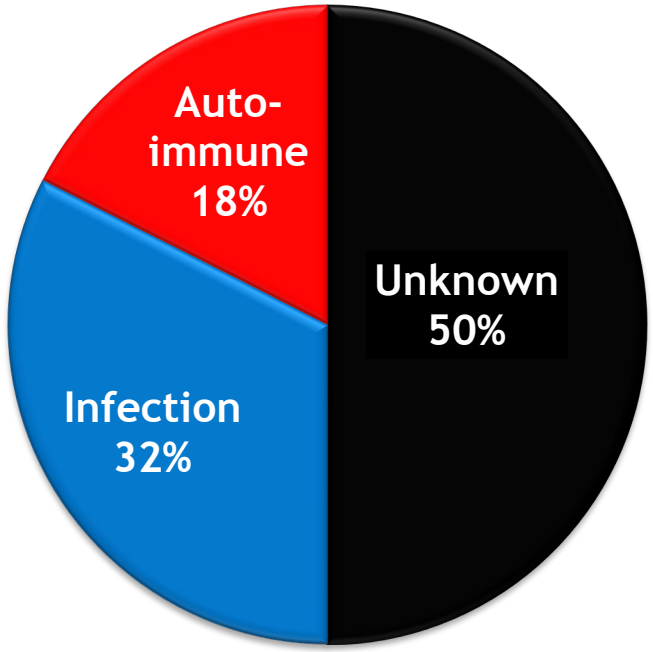
50% no cause-specific diagnosis

Viruses, bacteria, auto-immune disease

Mortality 15%, sequelae 50%

Treatment delay

Causes of encephalitis



Encephalitis

Table 1 Diagnostic criteria for encephalitis[a]
Major criterion (required)
Patients presenting to medical attention with altered mental status (defined as decreased or altered level of consciousness, lethargy, or personality change) lasting ≥24 hours with no alternative cause identified
Minor criteria (2 required for possible encephalitis; ≥3 required for probable or confirmed encephalitis)
Documented fever ≥38°C (100.4°F) within the 72 hours before or after presentation
Generalized or partial seizures not fully attributable to a preexisting seizure disorder
New onset of focal neurologic findings
CSF leukocyte count ≥5/mm^3
Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset
Abnormality on EEG that is consistent with encephalitis and not attributable to another cause.

Venkatesan et al, Clin Infect Dis 2013

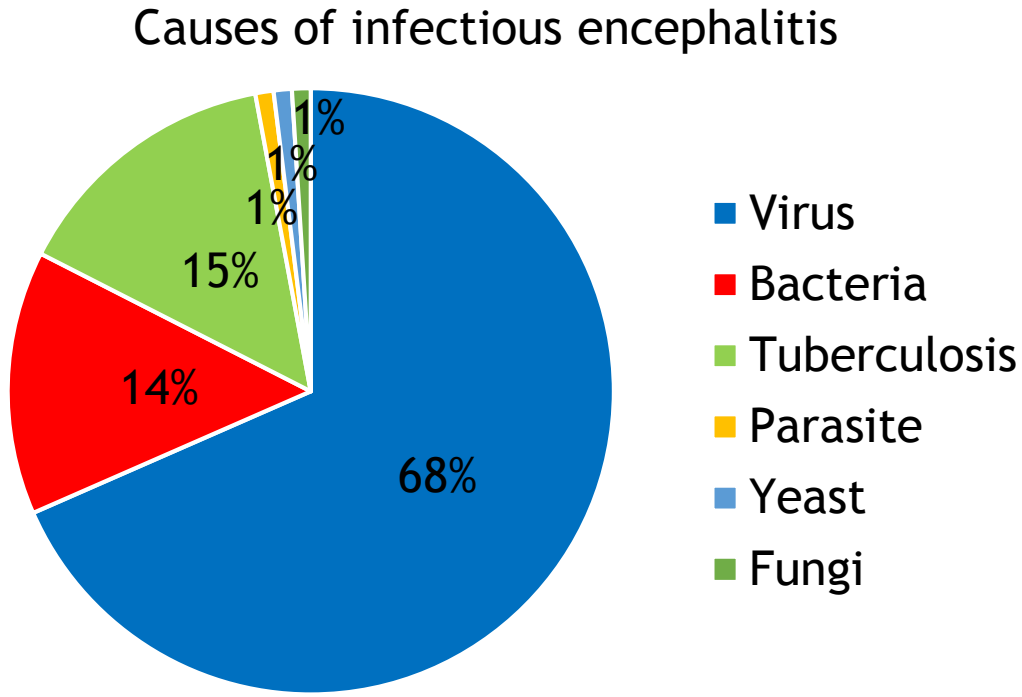
Infectious encephalitis

Some frequent causes

- HSV

- VZV / CMV

Many rare causes



Glaser et al, Clin Infect Dis 2003; Granerod et al, Lancet ID 2010; Mailles et al, Clin Inf Dis, 2009;

Infectious encephalitis

HSV most frequently identified cause of encephalitis

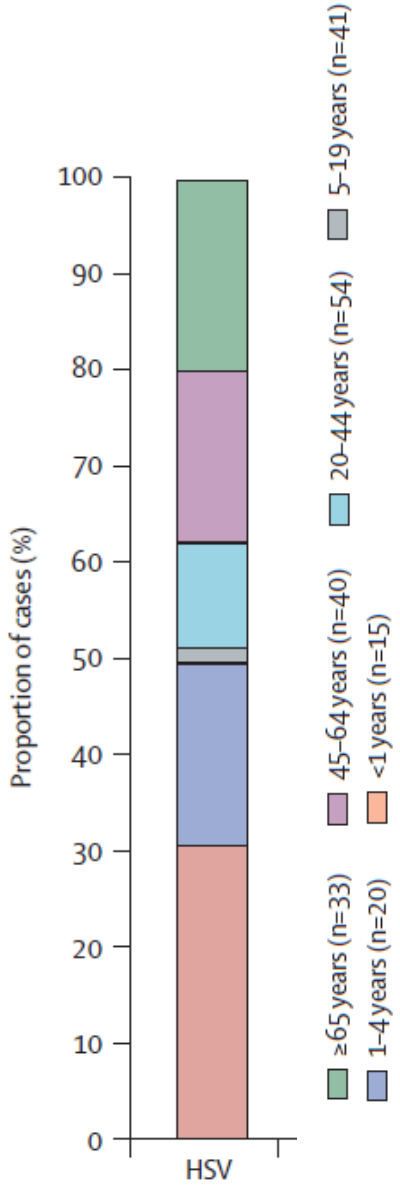
19% of cases

Incidence 2 to 5 per milion inhabitants

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

	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

Granerod et al, Lancet Infect Dis 2010



Herpes encephalitis

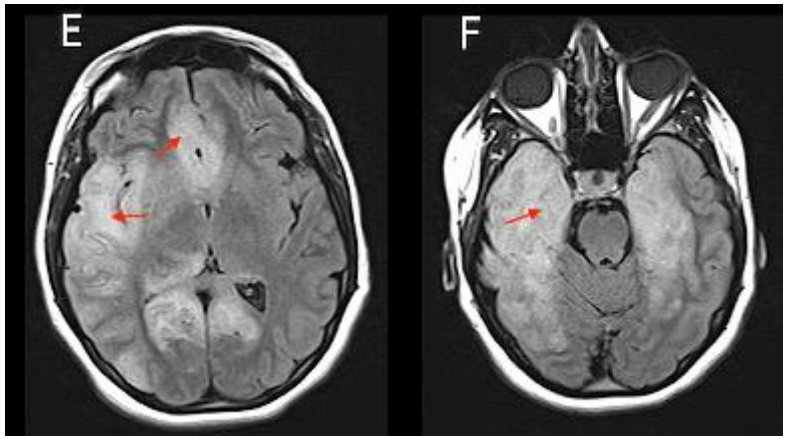
Characteristics	N=38	Characteristics	N=38
Fever	76%	Gastrointestinal	34%
Headache	42%	Respiratory	13%
Seizures	63%	Rash	5%
‘Lethargy’	42%	CSF pleiocytosis >4	80%
Neck stiffness	13%	CSF protein >0.50	63%
Focal neurology	42%	CSF:blood ratio <0.50	35%
Coma	24%		

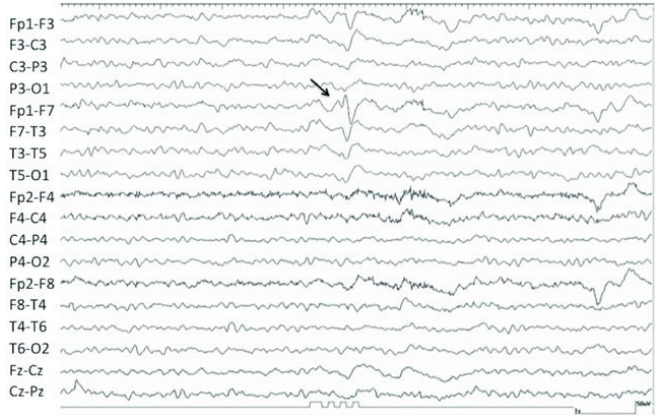
Herpes encephalitis: Ancillary investigations

Cranial CT	30% abnormal
Cranial MRI	89% abnormal
EEG	81% abnormal

CT

MRI





Herpes encephalitis

Diagnostic pitfalls

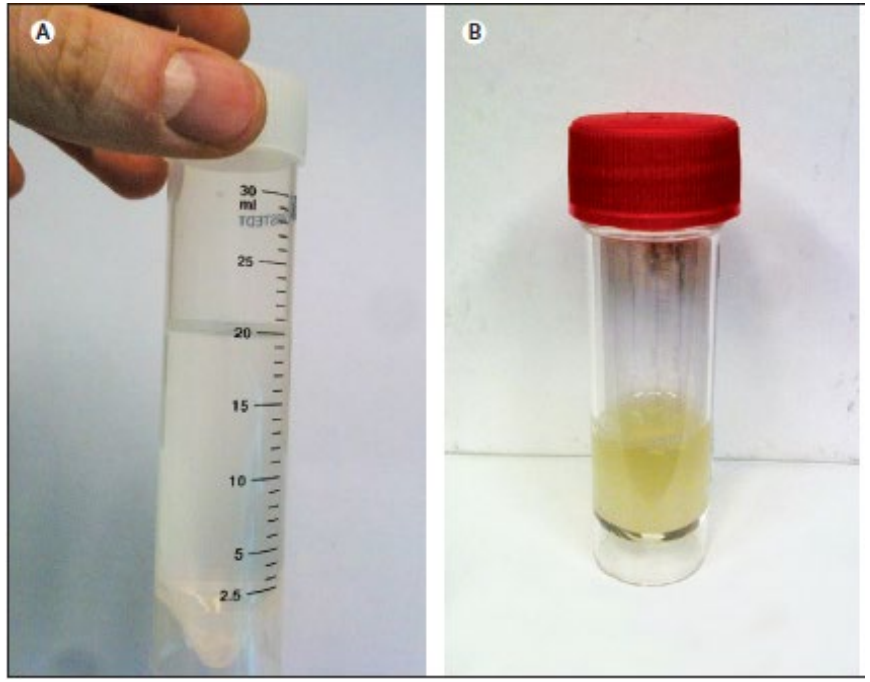
- Normal leukocyte count CSF 10-20%
- Negative PCR 5% patients

Persistent clinical suspicion *and*

no other cause identified

Repeated CSF examination day 3-7

- 2 negative PCRs >99% sensitivity



Back to Spain

It may very well be HSV encephalitis

Repeat the CSF examination

→ Positive PCR HSV

Next question

Do we need to treat with dexamethasone?

How long should we treat with acyclovir?

Treatment

Aciclovir tested in randomized controlled trial

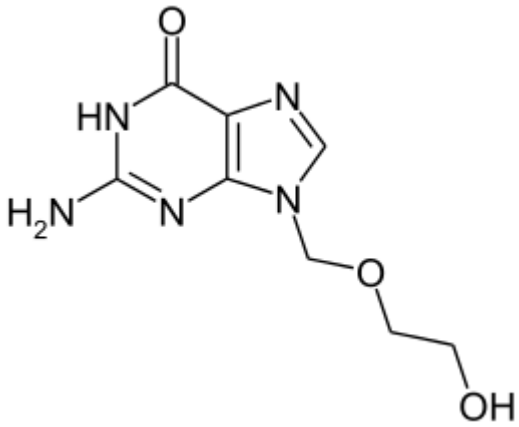
69 brain biopsy proven HSV encephalitis

37 vidarabine vs 32 acyclovir

10 mg/kg/TID

Treatment 10 days

Mortality 54% vs. 28%



Whitley et al, N Engl J Med 1986

Treatment

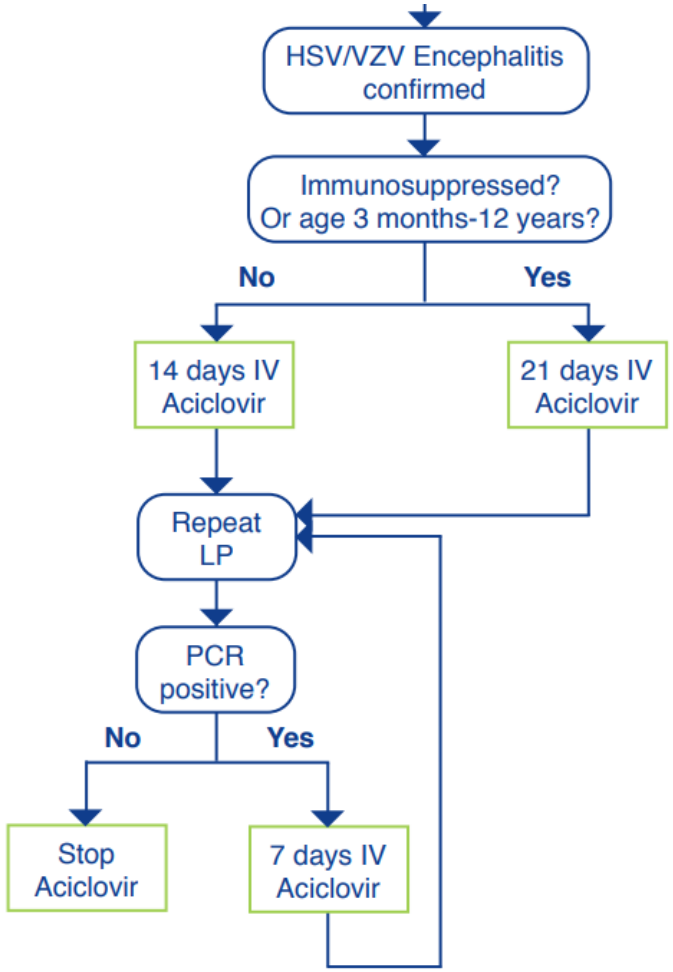
Duration of treatment 10, 14 or 21 days?

No comparative trials

‘Relapse’ HSV ~8% when treated for 10 days

No relapse after 21 days of treatment

Negative PCR associated with better outcome



Treatment protocol encephalitis society, J Inf 2012;64:347-73

Dexamethasone

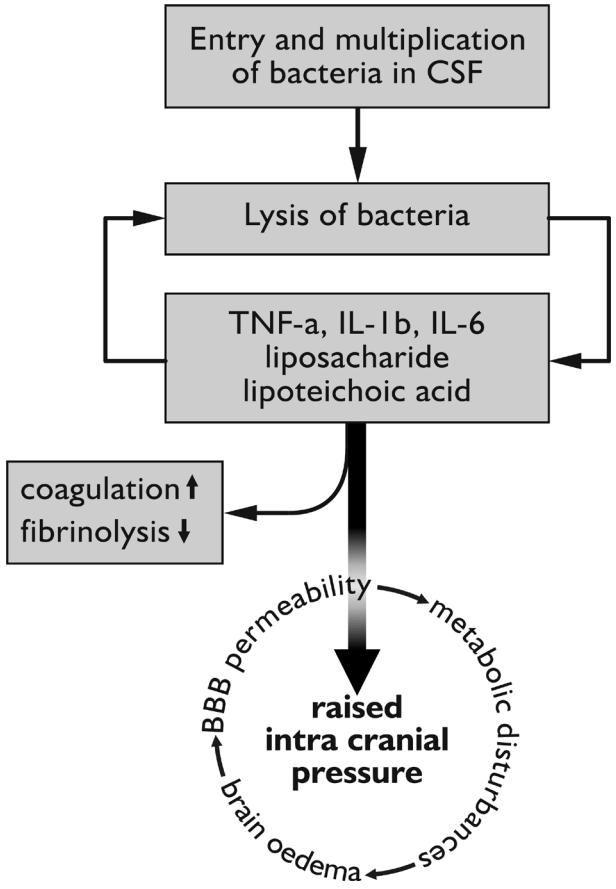
Reduction of inflammatory respons

Beneficial in bacterial meningitis & tuberculous meningitis

Harmful in cryptococcal meningitis

Retrospective case series: potential benefit

GACHE trial DXM in HSV encephalitis



Brouwer et al, Cochrane 2015; Nguyen et al N Engl J Med 2007; Beardsley et al N Engl J Med 2016

Dexamethasone RCTs

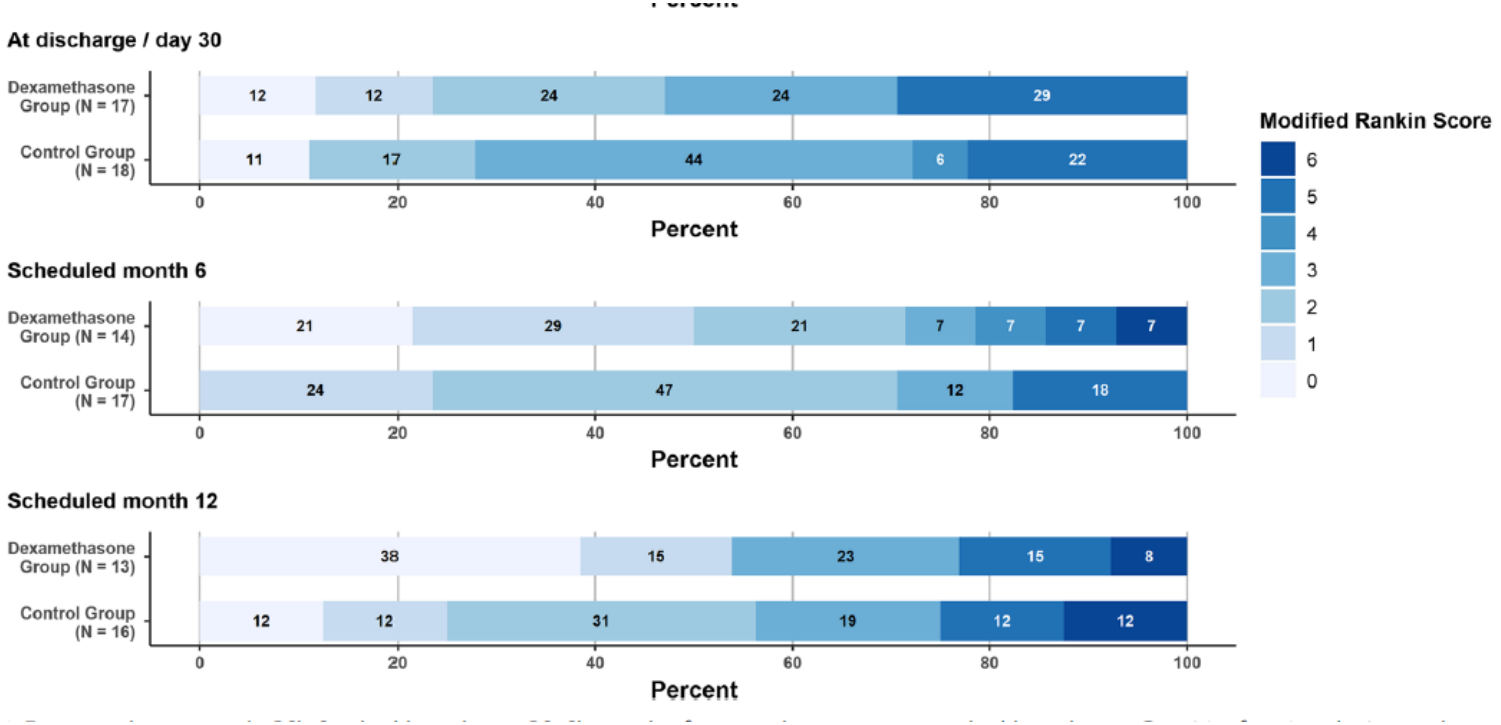
GACHE trial DXM in HSV encephalitis

Powered 372 patients

2007-2012 inclusion 38 pts

No significant difference

No harm



Meyding-Lamada et al, Neurol Research Pract 2019

Dexamethasone RCTs

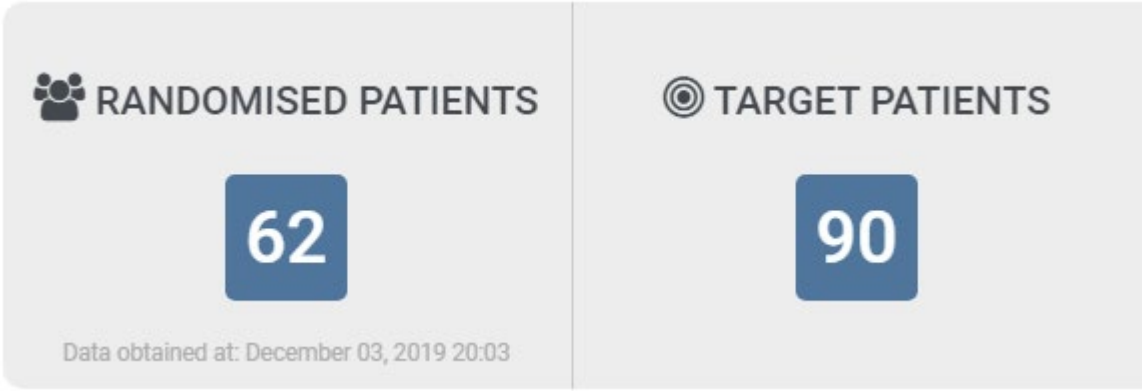
DexEnceph trial

RCT dexamethasone vs placebo

10mg QID for 4 days

Primary endpoint neuropsychological deficits

Currently ongoing



Back in the Netherlands

8 weeks later

Recovery to independency in activities of daily living

Cognitive defects persist, recovery has stagnated

Not able to restart study at university

Reevaluation outpatient clinic:

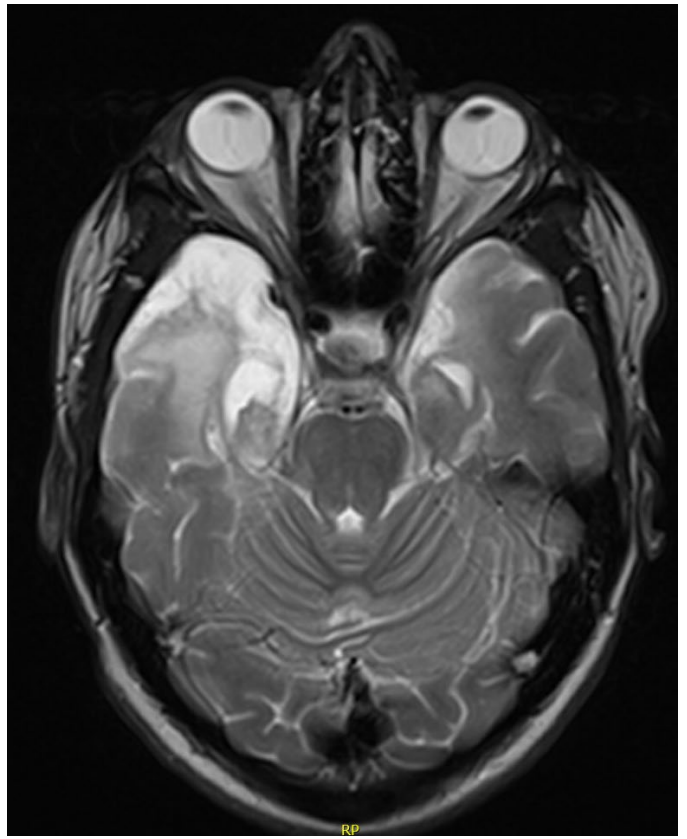
- Patient comes in and gives docter a hug
- Desinbition, fidgety

Could it be a relaps or something else?

Ancillary investations

Cranial MRI

CSF 60 leukocytes, protein 0,79 g/L

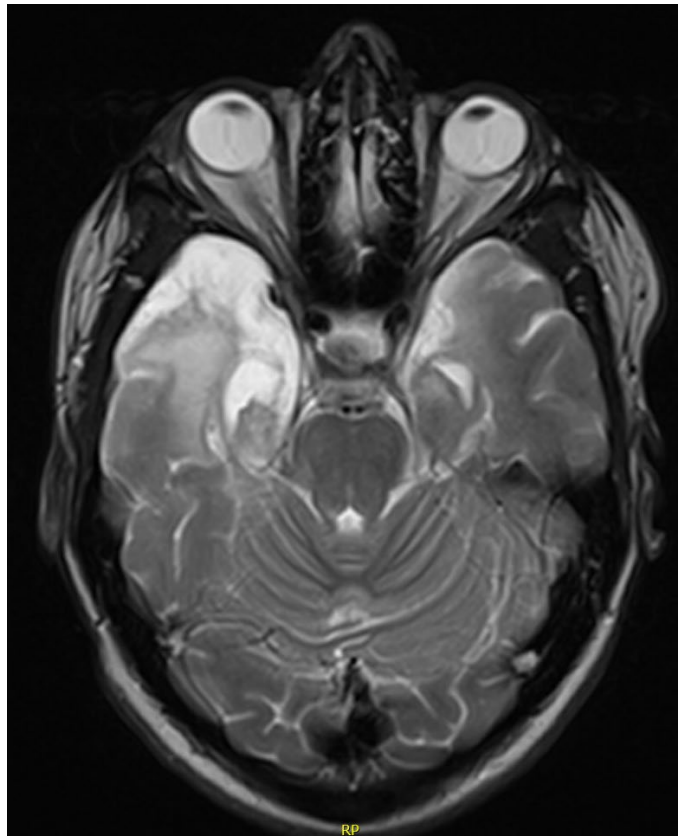


Ancillary investations

Cranial MRI

CSF 60 leukocytes, protein 0,79 g/L

PCR HSV negative



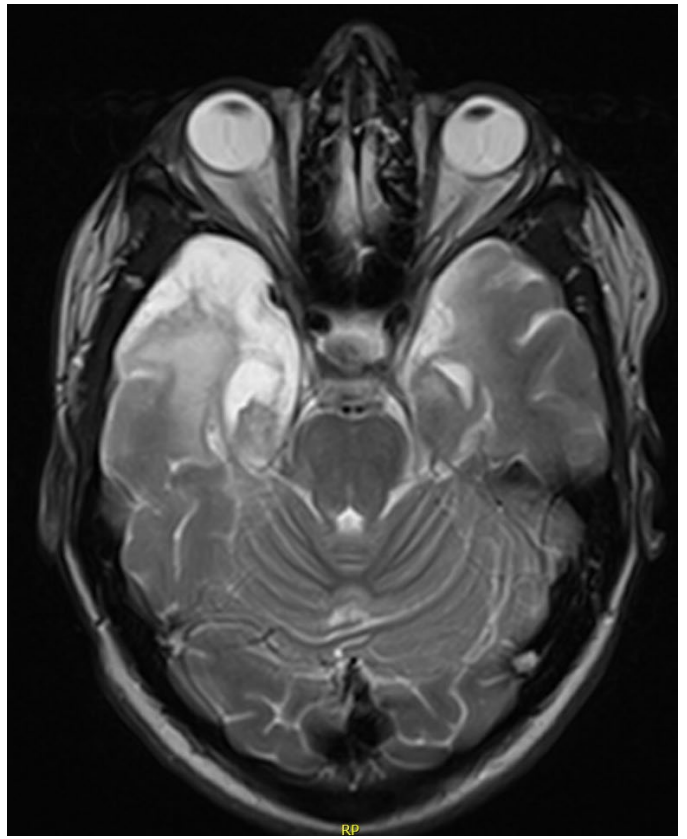
Ancillary investations

Cranial MRI

CSF 60 leukocytes, protein 0,79 g/L

PCR HSV negative

Anti NMDA-receptor antibodies strongly positive blood and CSF



Post-infectious anti-NMDA-receptor encephalitis

5-26% ‘relapse’ in HSV encephalitis

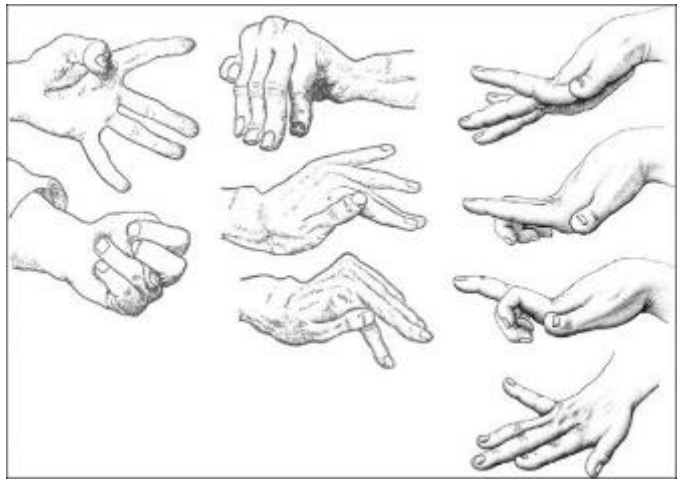
Viral testing often negative

Acyclovir ineffective

Choreoathetosis

- present in anti NMDA-R encephalitis & late complication of HSV
- immunotherapie useful in treatment of both

Same mechanism?



Post-infectious anti-NMDA-receptor encephalitis

Articles

Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis

*Thaís Armangue, Marianna Spatola, Alexandru Vlagea, Simone Mattozzi, Marc Cárceles-Cordon, Eloy Martinez-Heras, Sara Llufriu, Jordi Muchart, María Elena Erro, Laura Abraira, German Moris, Luis Monros-Giménez, Íñigo Corral-Corral, Carmen Montejo, Manuel Toledo, Luis Bataller, Gabriela Secondi, Helena Ariño, Eugenia Martínez-Hernández, Manel Juan, Maria Angeles Marcos, Laia Alsina, Albert Saiz, Myrna R Rosenfeld, Francesc Graus, Josep Dalmau, on behalf of the Spanish Herpes Simplex Encephalitis Study Group**

Lancet Neurol 2018; 17: 760–72
Published Online

Summary

Background Herpes simplex encephalitis can trigger autoimmune encephalitis that leads to neurological worsening. We aimed to assess the frequency, symptoms, risk factors, and outcomes of this complication.

Armangue et al Lancet Neur 2018

Post-infectious anti-NMDA-receptor encephalitis

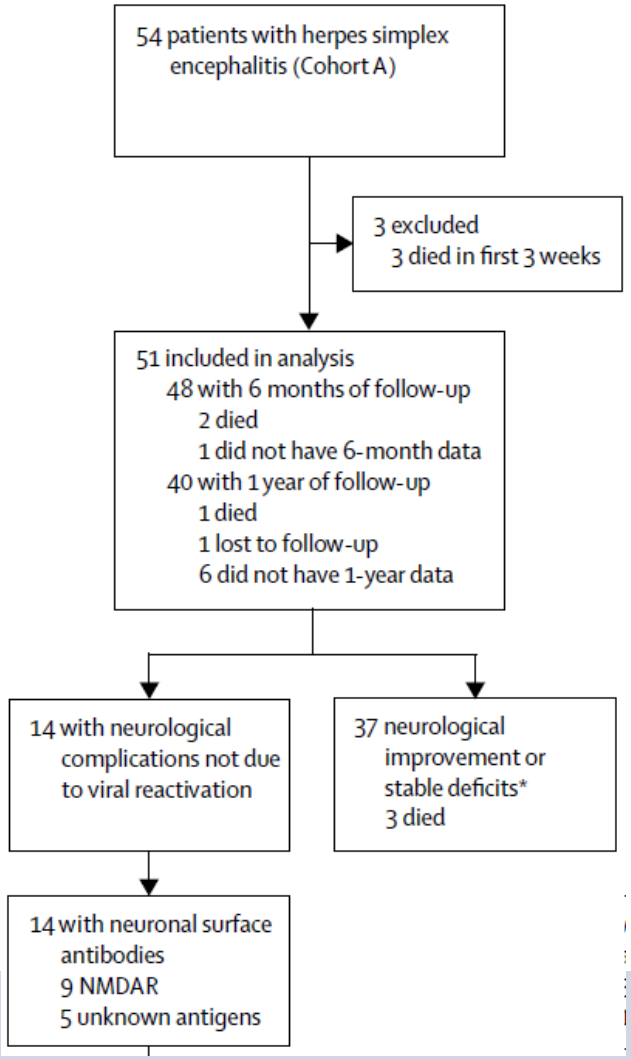
Prospective study

51 HSV encephalitis patients

14 (27%) auto-immune encephalitis

with auto-antibodies at 3 weeks

9 NMDAr antibodies



Armangue et al Lancet Neur 2018

Post-infectious anti-NMDA-receptor encephalitis

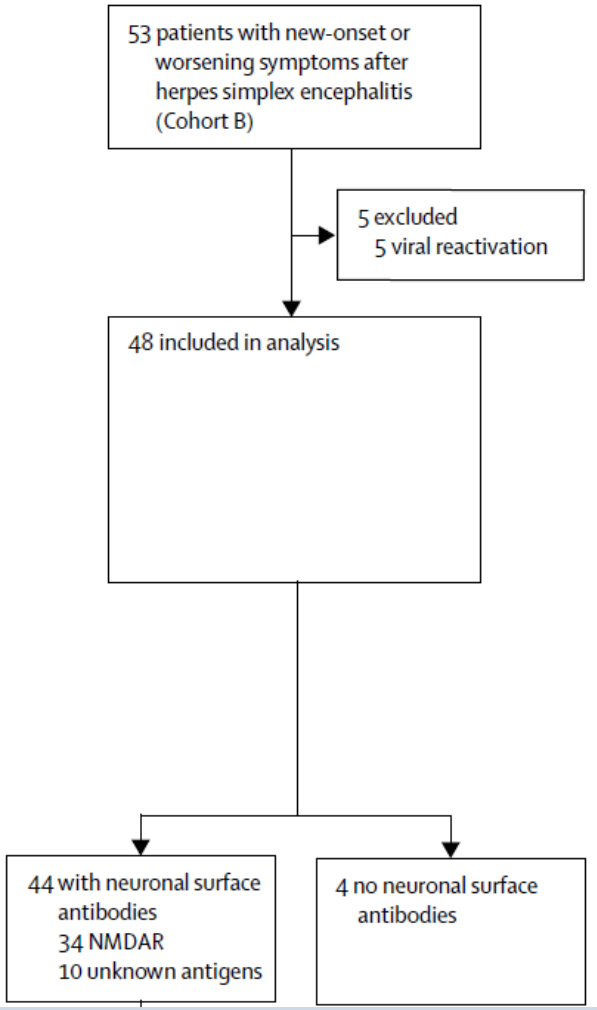
Retrospective study

48 patients new or persisting symptoms after HSV encephalitis

44 confirmed autoimmune encephalitis

34 anti-NMDAr antibodies

10 unknown antibodies



Armangue et al Lancet Neur 2018

Post-infectious anti-NMDA-receptor encephalitis

	All (N=51)	Autoimmune encephalitis after herpes simplex encephalitis		Comparison*
		Yes (n=14)	No (n=37)	
Median age, years	50 (5–68)	24 (0·9–75)	51 (13–68)	p=0·290
Younger children (≤4 years)	13 (25%)	6 (43%)	7 (19%)	p=0·089
Older children (5–17 years)	5 (10%)	1 (7%)	4 (11%)	p=0·182
Adults (≥18 years)	33 (65%)	7 (50%)	26 (70%)	p=0·182
Sex				
Women	22 (43%)	6 (43%)	16 (43%)	p=0·980
Men	29 (57%)	8 (57%)	21 (57%)	p=0·980
Symptoms during herpes simplex encephalitis				
Fever	49 (96%)	13 (93%)	36 (97%)	p=0·490
Altered consciousness	35 (69%)	11 (79%)	24 (65%)	p=0·335
Abnormal behaviour	21 (41%)	5 (36%)	16 (43%)	p=0·624
Memory deficits†	26/36 (72%)	6/8 (75%)	20/28 (71%)	p=0·841
Aphasia†	28/36 (78%)	7/8 (88%)	21/28 (75%)	p=0·431
Seizures	32 (63%)	11 (79%)	21 (57%)	p=0·139
Motor deficit	21 (41%)	8 (57%)	13 (35%)	p=0·156

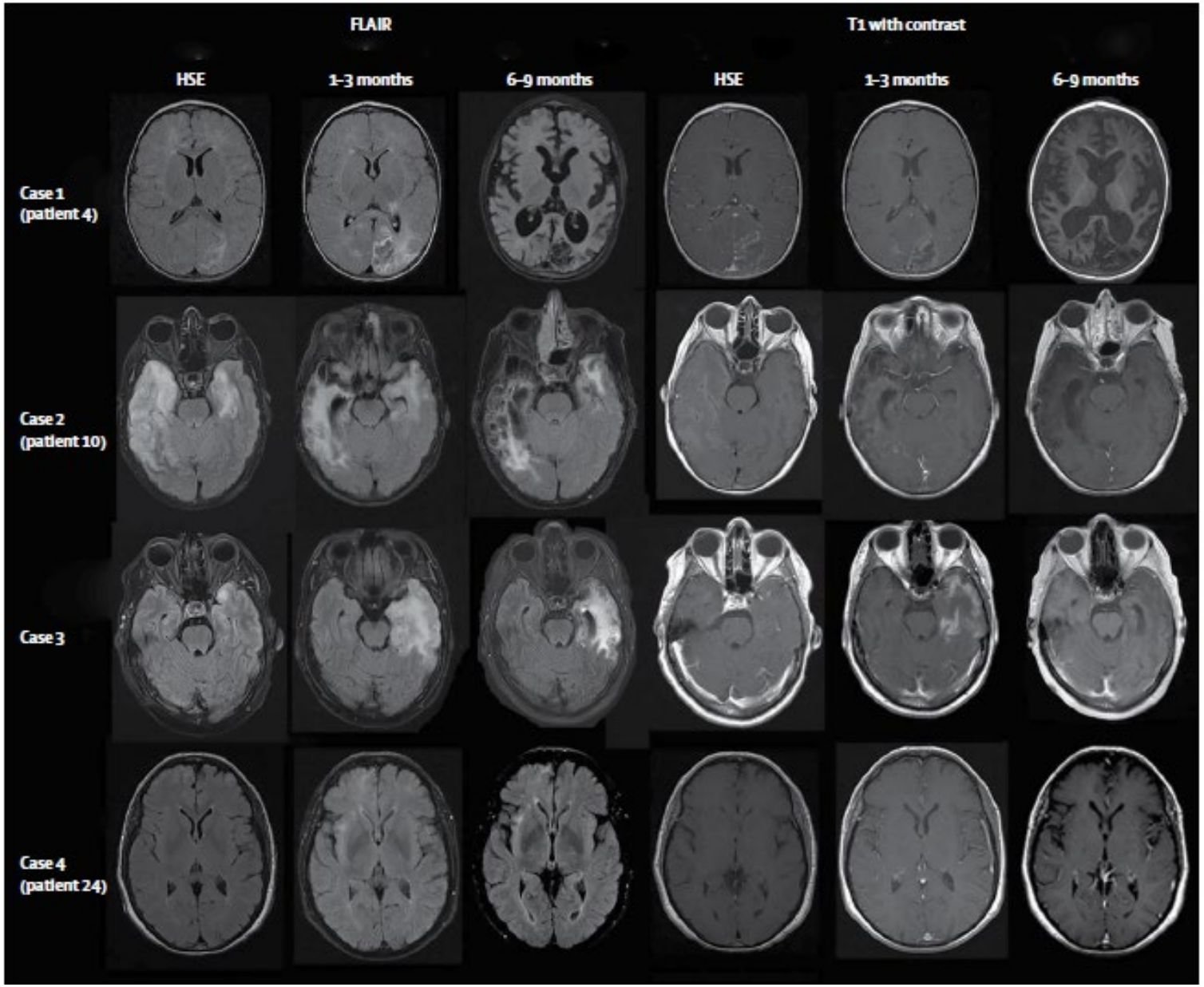
Armangue et al Lancet Neur 2018

1) HSV + NMDAr encephalitis

2) HSV + encephalitis unknown AB

3) HSV no autoimmune encephalitis

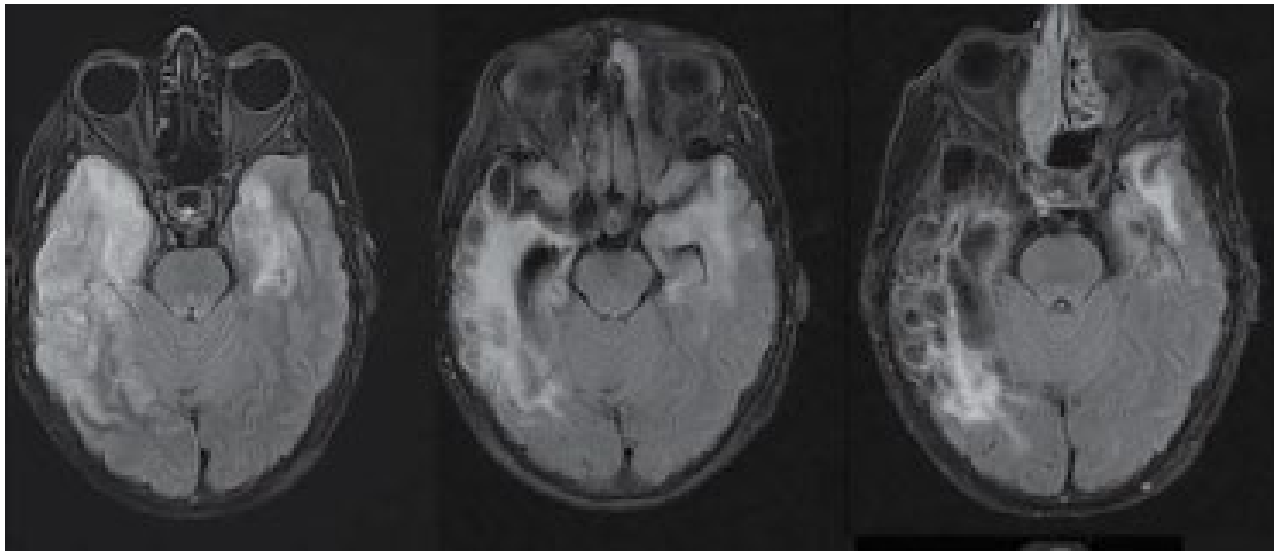
4) HSV + antibodies no encephalitis



Armangue et al Lancet Neur 2018

Cranial imaging

Area damaged brain ~ autoimmune antibodies / encephalitis



A

Patient	Sex	Age	Sample	HSE	Day 21	Day 60	Day 180	Day 365	Antigen	Serum titres	
										Highest*	Day 365
1	Male	2 months	CSF Serum	–	Day 7 +	+	+	+	NMDAR	1/3200	1/800
2	Male	3 months	CSF Serum	–	+	+	+	+	NMDAR	1/1600	1/400
3	Female	7 months	CSF Serum	–	+	+	+	+	NMDAR	1/12800	1/800
4	Male	11 months	CSF Serum	–	Day 19 +	+	+	+	NMDAR	1/3200	1/1200
5	Male	12 months	CSF Serum	–	+	+	+	–	NMDAR†	1/3200	Negative
6	Male	15 months	CSF Serum	–	+	+	+	+	NMDAR	1/3200	1/200
7	Male	13 years	CSF Serum	–	–	+	+	+	NMDAR	1/3200	1/400
8	Female	34 years	CSF Serum	–	–	–	–	–	NMDAR	1/200	Negative
9	Male	45 years	CSF Serum	–	+	–	–	–	NMDAR	(Only positive in CSF)	
10	Female	56 years	CSF Serum	–	–	–	–	–	Unknown	(Only positive in CSF)	
11	Female	75 years	CSF Serum	–	–	–	–	–	Unknown	(Only positive in CSF)	
12	Male	77 years	CSF Serum	–	+	+	+	+	Unknown	1/1600	1/800
13	Female	78 years	CSF Serum	–	Day 17 +	–	–	–	Unknown	(Only positive in CSF)	
14	Female	80 years	CSF Serum	–	–	–	Day 63 +	–	Unknown	(Only positive in CSF)	

mRS 0 mRS 1 mRS 2 mRS 3 mRS 4 mRS 5 Day of onset of autoimmune encephalitis

Armangue et al Lancet Neur 2018

Treatment

Mix of

- corticosteroids (i.v. MPS)
- Ivlg
- plasma exchange
- rituximab
- cyclophosphamide

Response to treatment unclear

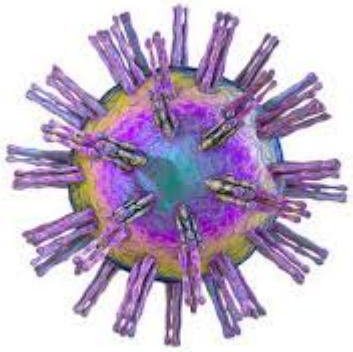
Modified Ranking Scale 3-5 after treatment, before ~5

Sequelae: anterograde amnesia, epilepsy, language disorders

Outcome

Mortality	11%
Severe disability	29%
Moderate disability	21%
Good recovery	39%
Length of hospital stay	~30 days

Conclusions



HSV encephalitis rare but severe

Treat upon suspicion

Negative PCR with clinical suspicion → continue treatment, repeat LP

Duration of acyclovir treatment 21 days

Benefit dexamethasone unclear

27% autoimmmune encephalitis mostly a-NMDAr

Outcome still poor

Neuroinfections Amsterdam

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Neuroinfections Amsterdam

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