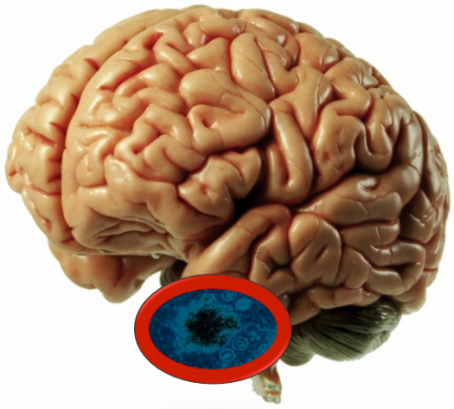
CHU de Poitiers

faculté de médecine et de pharmacie

Université de Poitiers

Encéphalite Herpétique

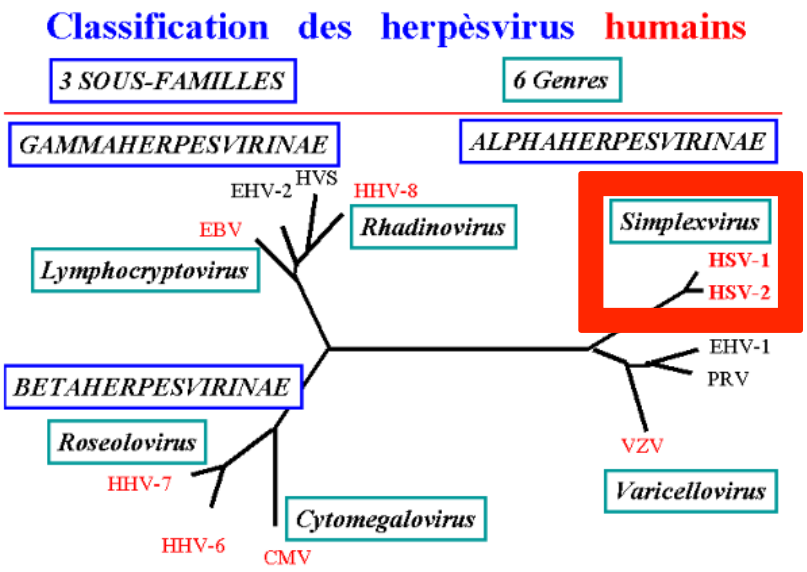


Olivier COLIN
DES Neurologie
14 mars 2014

Herpès (HSV) : 2 000 ans d'histoire

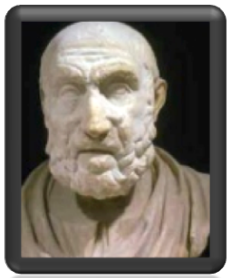
Herpes viridiae
300 millions d'années…

Grec « ἕρπης »
« herpein » : ramper



- Hippocrate (460-370 avant JC)

  éruption chronique vésiculeuse rampant sous la peau



- Tibère (42 avant JC)

  juguler épidémie herpès labial

Encéphalite herpétique

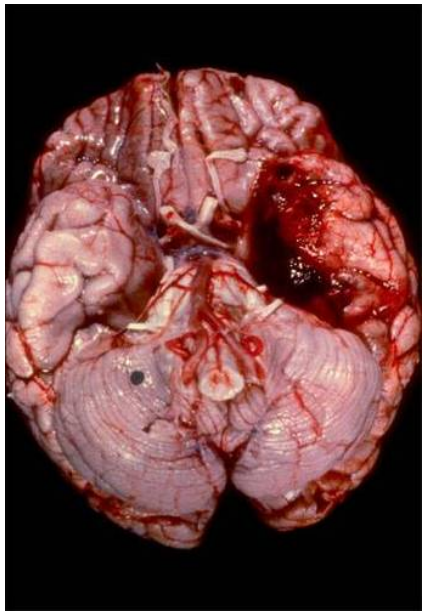
Polioencéphalite aiguë nécrosante et hémorragique

affectant de manière bilatérale et asymétrique les lobes temporaux et parfois l'insula et les régions frontales

Gravité

15% de décès à 6 mois

80% mortalité sans traitement



Raschilas et al. Clin Infect Dis 2002

BMJ

BMJ 2012;344:e3166 doi: 10.1136/bmj.e3166 (Published 6 June 2012)

PRACTICE

EASILY MISSED?

Herpes simplex encephalitis

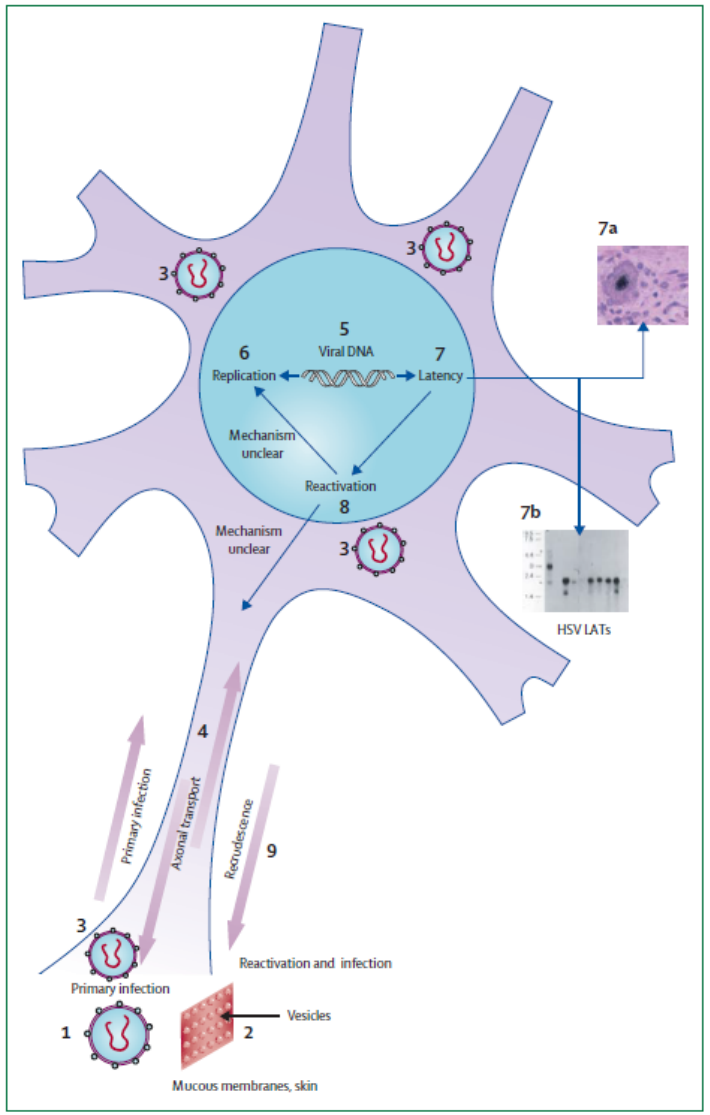
Mazen Sabah *neurology specialist registrar*[1], James Mulcahy *consultant physician*[2], Adam Zeman *professor of cognitive and behavioural neurology*[3]

Key points

- Herpes simplex encephalitis is highly treatable, but can cause death or severe neuropsychological impairment if untreated
- The diagnosis is suggested by acute or subacute onset of
  Alterations of behaviour
  Focal or generalised seizures
  Focal neurological signs
  Cognitive difficulties
  Usually on a background of fever and headache
- If it is suspected perform urgent brain imaging (preferably magnetic resonance imaging) and cerebrospinal fluid analysis for microscopy and DNA testing (if lumbar puncture is not contraindicated), bearing in mind that these may be normal early in the course of the disease
- Start intravenous aciclovir immediately if the diagnosis is suspected

ME : HSV 1 (et HSV 2)

- Virus à ADN / cycle de réplication rapide
- Etat de latence : tropisme neuronal
  - après PI pharyngée ou sexuelle
  - neurones ganglionnaires sensitifs territoire PI
  - Gasser (trijumeau) HSV 1/ Sacrés HSV 2
- Deux types antigéniquement différents
  - HSV-1 (95%) et HSV-2 (5%)
- Réservoir
  - homme (le seul)
  - contagion strictement interhumaine
- Deux mécanismes pathogènes imbriqués
  - cytotoxicité virale
  - réaction immunopathologique
    - destruction et nécrose cellulaire



Controverses

Herpes simplex virus encephalitis: new infection or reactivation?

Israel Steiner

Department of Neurology, Rabin Medical Center, Petach Tikva, Israel

Correspondence to Dr Israel Steiner, MD, Department of Neurology, Rabin Medical Center, Beilinson Campus, 49100 Petach Tikva, Israel
Tel: +972 3 9376351; e-mail: isteiner@cc.huji.ac.il

Current Opinion in Neurology 2011, 24:268–274

Purpose of review

This review describes the pathogenesis, clinical presentation, course, and therapy of herpes simplex encephalitis (HSE), the most fatal viral encephalitis, in which prognosis is dependent on early diagnosis and effective therapy.

Recent findings

Herpes simplex viruses types 1 and 2 (HSV-1 and HSV-2) are human neurotropic viruses that establish latent infection in dorsal-root ganglia for the entire life of the host. From this reservoir, they can reactivate to cause human morbidity and mortality. HSE is one of the most devastating disorders caused by these viruses. The biology of their ability to establish latency, maintain it for the entire life of the host, reactivate, and cause primary and recurrent disease is being studied in animal models and in humans. Of special interest is the question whether HSE is the result of primary infection or is it the outcome of reactivation. The present review covers the biological, medical, and neurological aspects of HSE, focusing among others on recent molecular findings of gene expression during latent infection of HSV-1.

Summary

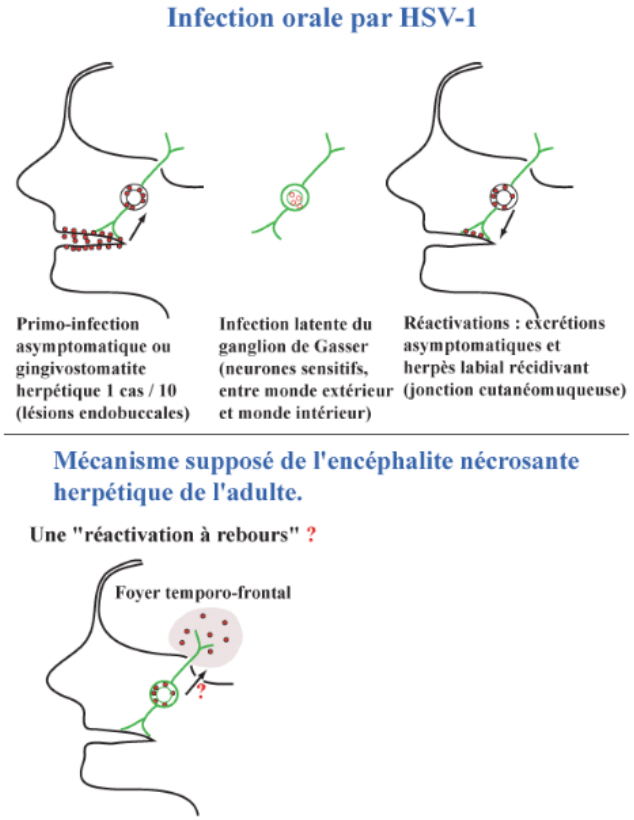
Despite accumulating knowledge, there are still several issues regarding both pathogenesis and therapy of HSV-1 that currently defy understanding.

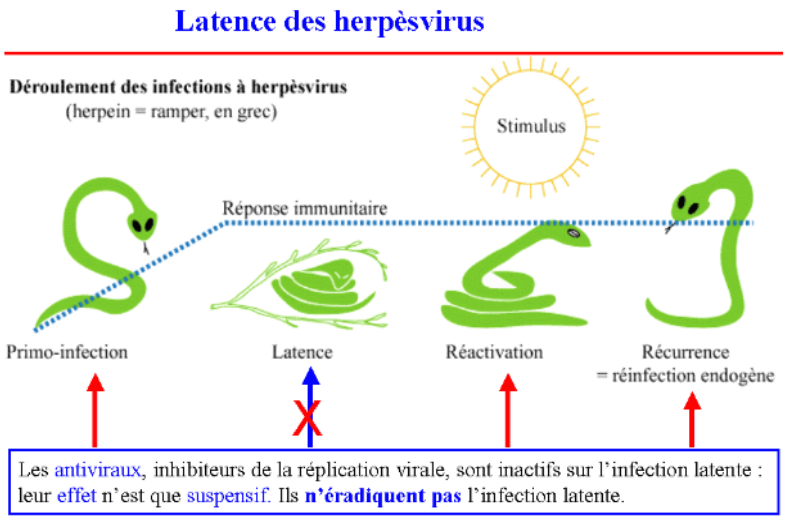
Facteurs de survenue ?

Personnes saines

Primo-infection SNC

Récurrence « à rebours » du ganglion de Gasser vers le lobe temporal ?





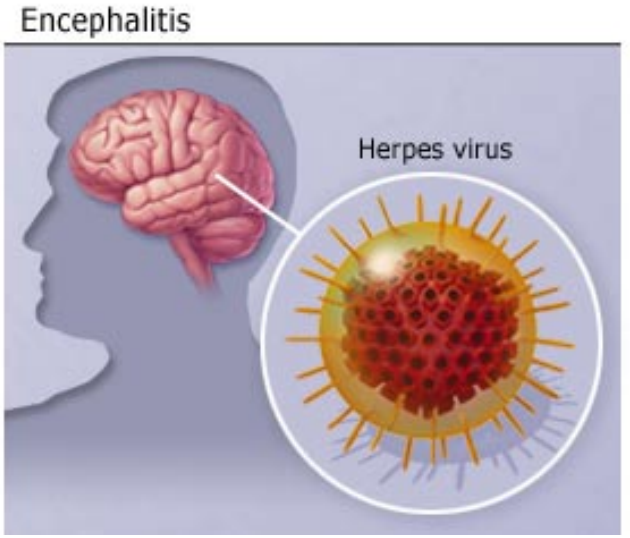
Steiner I and al. Lancet Neurol 2007

Fraser NW and al. Proc Natl Acad Sci 1981

Whitley RJ and al. N Engl J Med 1982

MEH : épidémiologie

- Infection endémique
- Incidence chez l'adulte
  - 1/100 000 à 1/500 000 par an
- Age moyen de survenue = 40 ans



Méningo-encéphalite adulte : HSV-1
HSV-2 (NN – nourrisson :filière génitale)

Raschilas F and al. Clin Infect Dis 2002

Infectious Encephalitis in France in 2007: A National Prospective Study

Alexandra Mailles[1] and Jean-Paul Stahl,[2] on behalf of the Steering Committee and the Investigators Group[a]

[1]Institut de Veille Sanitaire, Saint-Maurice, and [2]Infectious Diseases Unit, University Hospital of Grenoble, Grenoble, France

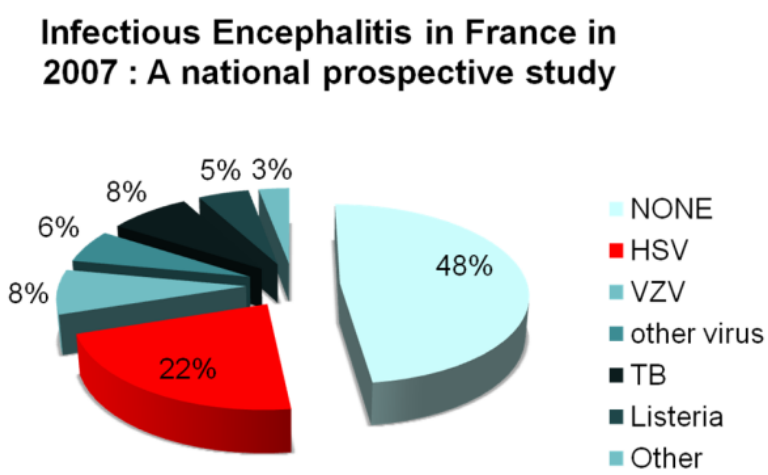
(See the editorial commentary by Glaser and Bloch, on pages 1848–50.)

Background. Encephalitis is associated with significant mortality and morbidity, but its cause remains largely unknown. We designed a national prospective study in France in 2007 to describe patients with encephalitis, investigate the etiologic diagnosis of encephalitis, and assess risk factors associated with death.

Methods. Patients were enrolled by attending physicians according to case definition, and data were collected with a standardized questionnaire. The etiologic diagnosis was investigated after a standardized procedure. Risk factors associated with death during hospitalization were assessed by multivariate logistic regression.

Results. A total of 253 patients with acute infectious encephalitis from 106 medical units throughout France were included in the study. Their ages ranged from 1 month to 89 years (median age, 54 years); 61% were male. Cause of the encephalitis was determined in 131 patients (52%). Herpes simplex virus 1 (42%), varicella-zoster virus (15%), *Mycobacterium tuberculosis* (15%), and *Listeria monocytogenes* (10%) were the most frequently identified agents. Twenty-six patients (10%, all adults) died, 6 of them with tuberculosis and 6 with listeriosis. Risk factors independently associated with death during hospitalization identified by the multivariable analysis were age (odds ratio [OR], 1.2; 95% confidence interval [CI], 1.0–1.4; for 5-year increase), cancer (OR, 17; 95% CI, 2.3–122.6), immunosuppressive treatment before onset (OR, 24; 95% CI, 1.3–426.0), percentage of hospitalized patients receiving mechanical ventilation (OR, 2.0; 95% CI, 1.4–3.0; for 10% increase), the etiologic agent, coma on day 5 after admission (OR, 16; 95% CI, 2.8–92.3), and sepsis on day 5 after admission (OR, 94; 95% CI, 4.9–1792.2).

Conclusions. Our prospective study provides an overview of the clinical and etiologic patterns of acute infectious encephalitis in adults in France. Herpes simplex virus 1 remains the main cause of encephalitis, but bacteria accounts for the highest case-fatality rates.



Clinical Infectious Diseases 2009; 49:1838–47

1058-4838/2009/4912-0010$15.00
DOI: 10.1086/648419

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.

Findings We identified 203 patients with encephalitis. Median age was 30 years (range 0–87). 86 patients (42%, 95% CI 35–49) had infectious causes, including 38 (19%, 14–25) herpes simplex virus, ten (5%, 2–9) varicella zoster virus, and ten (5%, 2–9) *Mycobacterium tuberculosis*; 75 (37%, 30–44) had unknown causes. 42 patients (21%, 15–27) had acute immune-mediated encephalitis. 24 patients (12%, 8–17) died, with higher case fatality for infections from *M tuberculosis* (three patients; 30%, 7–65) and varicella zoster virus (two patients; 20%, 2–56). The 16 patients with antibody-associated encephalitis had the worst outcome of all groups—nine (56%, 30–80) either died or had severe disabilities. Patients who died were more likely to be immunocompromised than were those who survived (OR=3·44).

Interpretation Early diagnosis of encephalitis is crucial to ensure that the right treatment is given on time. Extensive testing substantially reduced the proportion with unknown cause, but the proportion of cases with unknown cause was higher than that for any specific identified cause.

	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**

Lancet Infect Dis, 2010

MEH : Manifestations Cliniques

SYNDROME INFECTIEUX

fièvre presque constante (96%)

+

SYNDROME MÉNINGÉ

(inconstant <50 % des cas, rarement franc, se limitant à des céphalées fébriles)

+

SYNDROME ENCÉPHALITIQUE

(inflammation de l'encéphale, traduisant un dysfonctionnement du SNC)

TROUBLES DE LA VIGILANCE OU DE LA CONSCIENCE (86%)

Quasi constants, fluctuants : souffrance cérébrale diffuse
Troubles neurovégétatifs (pouls, PA, température)

MANIFESTATIONS COMITIALES (33%)

Un des motifs les plus fréquents
Partielles *lobe temporal* (illusions, hallucinations) >>> Généralisées

MODIFICATIONS DU COMPORTEMENT / TROUBLES MNÉSIQUES OU PHASIQUES

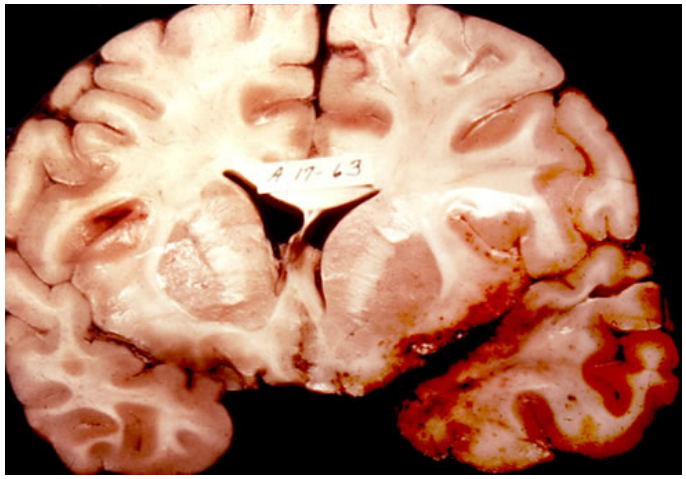
Familiarité, agressivité, ludisme (45%)
Mécanismes de fixation avec oubli à mesure (69%)
Troubles du langage (manque du mot ou aphasie amnésique) (59%)

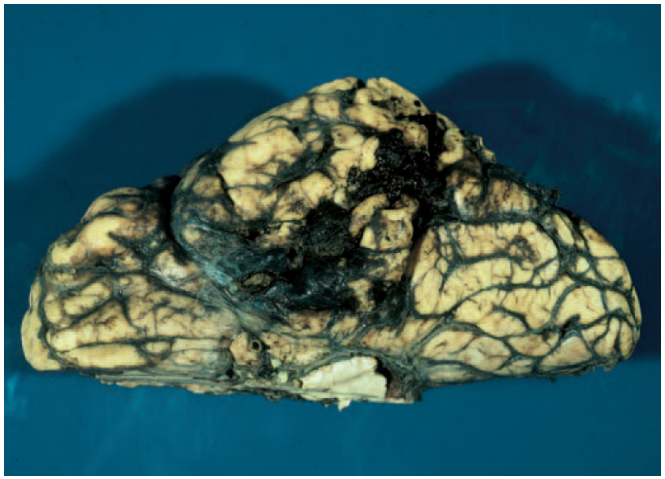
→ *L'instabilité hémodynamique est liée à l'atteinte neurologique centrale le plus souvent*

Raschilas F and al. Clin Infect Dis 2002

Formes cliniques

- Modalités évolutives
  - (formes méningées pures ?)
  - formes graves conduisant au décès
  - formes récurrentes dans 5 % des cas





L'encéphalite herpétique est nécrosante…

Diagnostic différentiel

L'encéphalite herpétique est nécrosante…

Tableau III. – Affections pouvant simuler une méningoencéphalite herpétique [73, 74].

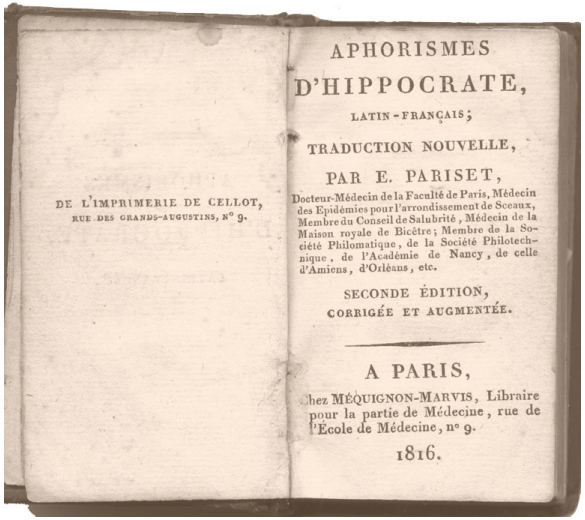
Virales	Arbovirus VZV, CMV, EBV Echovirus, Adénovirus, Coxsackievirus Paramyxovirus (grippe, oreillons)
Bactériennes	Listériose, Mycoplasme Rickettsiose, Coxiellose Mycobactéries Typhoïde Maladie de Whipple Méningite à méningocoque Abcès cérébral, empyème sous-dural
Parasitaires	Trypanosomiase, abcès amibien, accès pernicieux palustre Trichinose
Fongiques	Cryptococcose, Mucormycose
Autres	Encéphalopathie toxique ou métabolique Maladie de Behçet, LED, sarcoïdose neurologique Accident vasculaire cérébral Encéphalomyélite aiguë postinfectieuse Tumeur cérébrale

Houeto JL et Gout O, EMC Maladies infectieuses, 1999
Whitley RJ et al. N Engl J Med, 1990
Whitley RJ et al. JAMA 1999

Quels outils diagnostiques ?

Le diagnostic est « redouté » par la clinique

« Celui qui entre en fureur,
qui ne reconnaît personne,
n'entend plus, ne comprend plus,
approche de sa fin »



DE L'IMPRIMERIE DE CELLOT,
RUE DES GRANDS-AUGUSTINS, N° 9.

APHORISMES
D'HIPPOCRATE,
LATIN-FRANÇAIS;
TRADUCTION NOUVELLE,
PAR E. PARISET,
Docteur-Médecin de la Faculté de Paris, Médecin des Epidémies pour l'arrondissement de Sceaux, Membre du Conseil de Salubrité, Médecin de la Maison royale de Bicêtre; Membre de la Société Philomatique, de la Société Philotechnique, de l'Académie de Nancy, de celle d'Amiens, d'Orléans, etc.
SECONDE ÉDITION,
CORRIGÉE ET AUGMENTÉE.

A PARIS,
chez MÉQUIGNON-MARVIS, Libraire pour la partie de Médecine, rue de l'École de Médecine, n° 9.
1816.

Quels outils diagnostiques ?

PONCTION LOMBAIRE

d'emblée afin d'éviter tout retard dans la PEC thérapeutique
(imagerie en cas de signes de focalisation)

- Composition anormale LCR (98%)
  - Hyperprotéinorachie modérée (< 1 g/l) (98%)
  - Hypercytose lymphocytaire (< 500/mm3) (98%)
  - Souvent faiblement hémorragique (10 à 1 000 GR) (nécrose)
  - Glycorachie normale

  - *(Taux élevé d'interferon)*

Raschilas et al. Clin Infect Dis. 2002

PCR HSV

Examen de référence du diagnostic de ME herpétique

Powell KF and al. Lancet 1990
Rozenberg F and al. J Clin Microbiol 1990

- Se 98 % / Spé 94 %
  - ME herpétique prouvée - biopsie cérébrale

    Lakeman FD and al. J Infect Dis 1995

- Se (153/160) = 96%
  Spé (413/416) = 99%

  Tebas and al. Am J Med 1998

- Faux-négatifs possibles dans 1ers jours d'évolution

  Weil AA and al. Clin Infect Dis 2002

Polymerase Chain Reaction for Herpes Encephalitis/Tebas et al

Table 2. Studies Used to Determine the Sensitivity and Specificity of PCR for Herpes Simplex Encephalitis

	Number of Subjects	Herpes Encephalitis Present (n = 160)		Herpes Encephalitis Not Present (n = 416)	
		PCR+	PCR−	PCR+	PCR−
Lakeman et al (20)	101	53	1	3	44
Aurelius et al (5)	130	41	2	0	87
Rozenberg et al (8)	65	27	1	0	37
Kessler et al (16)	123	16	0	0	107
Klapper et al (6)	22	9	1	0	12
Puchammer-Stockl et al (7)	20	4	1	0	15
Troendle-Atkins et al (11)	115	3	1	0	111
Total	576	153	7	3	413

PCR = polymerase chain reaction.

Et si la PCR HSV est négative ?

Trop précoce ?

- CAT ?
  - 2ème PCR (positivité parfois retardée de 4 jours)
  - Si cette 2ème PCR est négative
    - hypothèse diagnostique est éliminée
    - traitement aciclovir peut être interrompu (PCR négative entre J4 et J10)

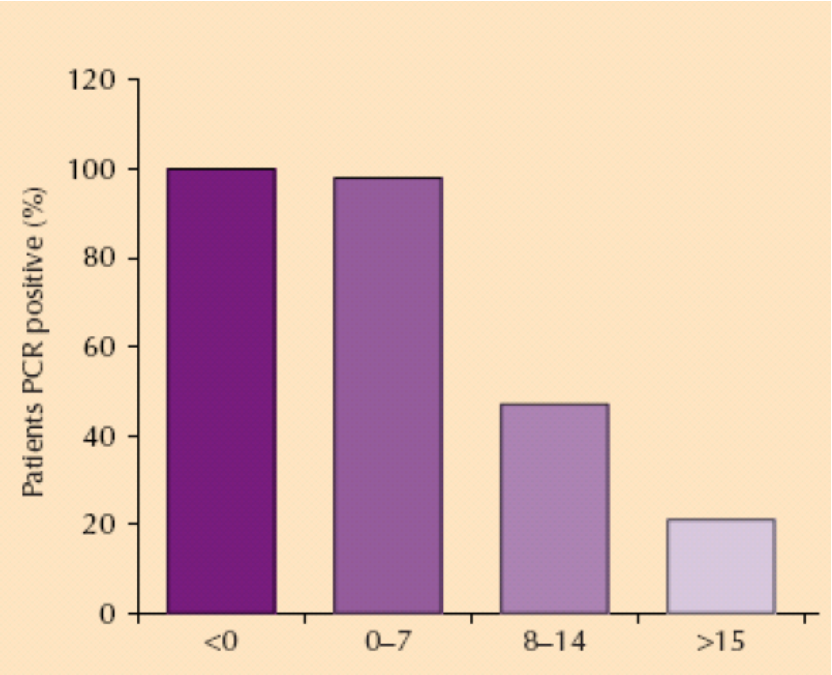
« Le contrôle dans les 4 jours après la première PL est positif en cas de MEH »

Guffond T et al. CID 1994
Studahl M et al. Scand J Infect Dis 1998

- Et en sanguin ?
  - Recherche d'antigènes herpétiques :
    - + précocement, mais technique peu sensible
  - Recherche d'anticorps dans le sang (IgM)
    - très spécifique, mais positivité tardive
  - Séroconversion
    - 8 jours après l'apparition des signes cliniques
    - trop tard pour le traitement

Sous traitement Aciclovir ?

Proportion PCR HSV +
sous traitement antiviral



Whitely, J Infect Dis 1995

Quels outils diagnostiques ?

Electroencéphalogramme

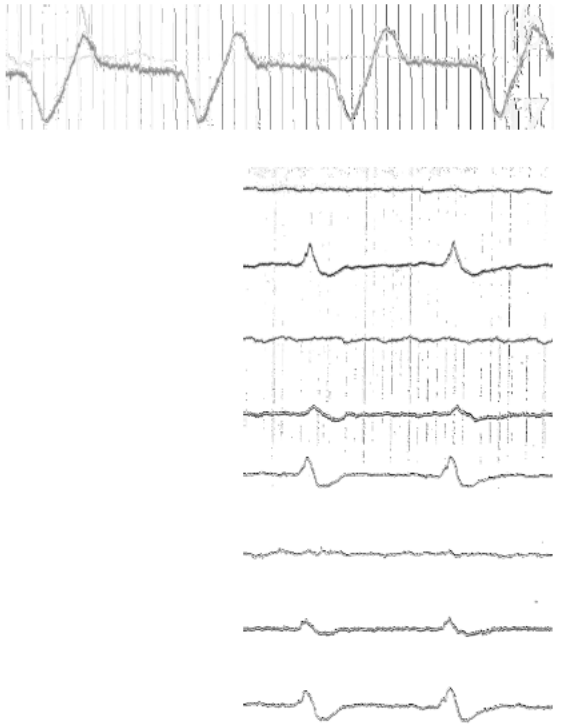
Se 84% / Spe 33%

Whitely, Antiviral Research, 2000

J0-J2

Ralentissement EEG, souvent lent ++, temporal, asymétrique

J2-J6 : activité périodique focale à périodicité courte



Ondes mono ou diphasiques, à front raide
de grande amplitude, de longue durée (1 – 1.5 s)
Pseudo périodiques (2-4 s)
Morphologie variable mais stable chez un sujet donné
Prédominance temporale
Non permanentes
Diffusion secondaire

J 15

Disparition (nécrose)

Quels outils diagnostiques ?
IRM cérébrale

Bonne sensibilité (24–48 heures) avec coupes T1 + injection de gadolinium et T2 et f

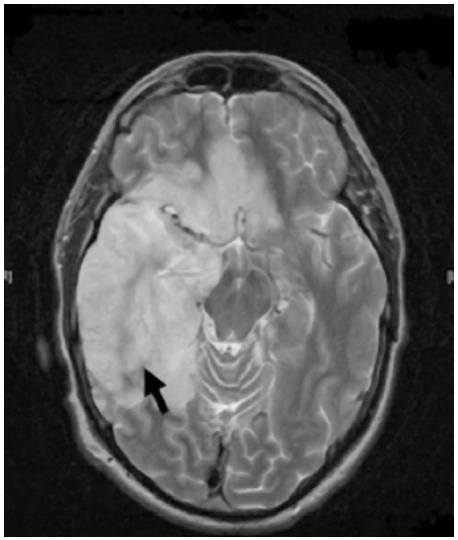
Limite : compliance du patient (sédater)

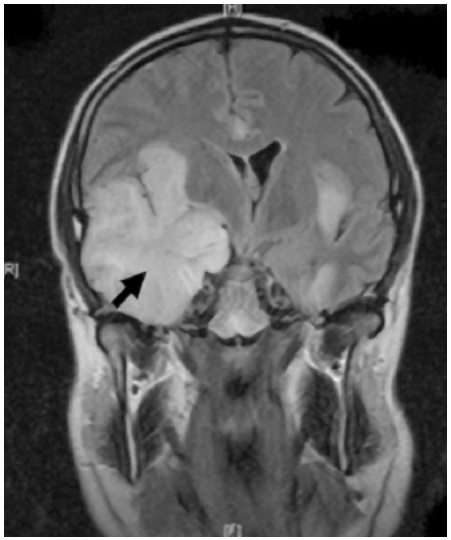
- Hypersignaux T2 et T2F
  - pôle temporal antérieur et progression vers le lobe temporal moyen et interne
  - topographie bilatérale et asymétrique
  - gadolinium : affinité HSV cortex hippocampique, parahippocampique et insulaire

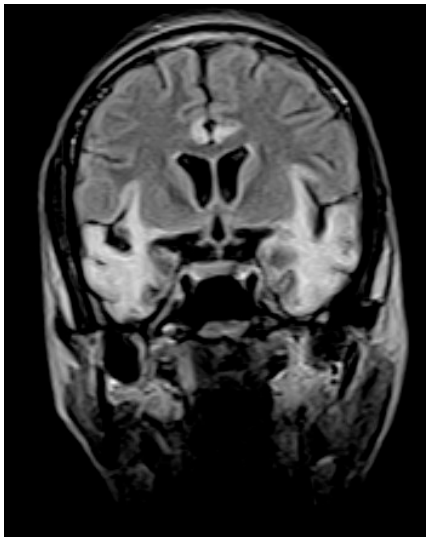
- Evolution : M3 - M12 : atrophie d'un ou des deux noyaux amygdalien +/- atrophie hippocampique

Facteur pronostic péjoratif : hypersignaux étendus lobes temporaux 1 à 2 mois après la phase aiguë

Kuker W and al. Neuroradiology 2004







The British Journal of Radiology, 85 (2012), e782–e792

REVIEW ARTICLE

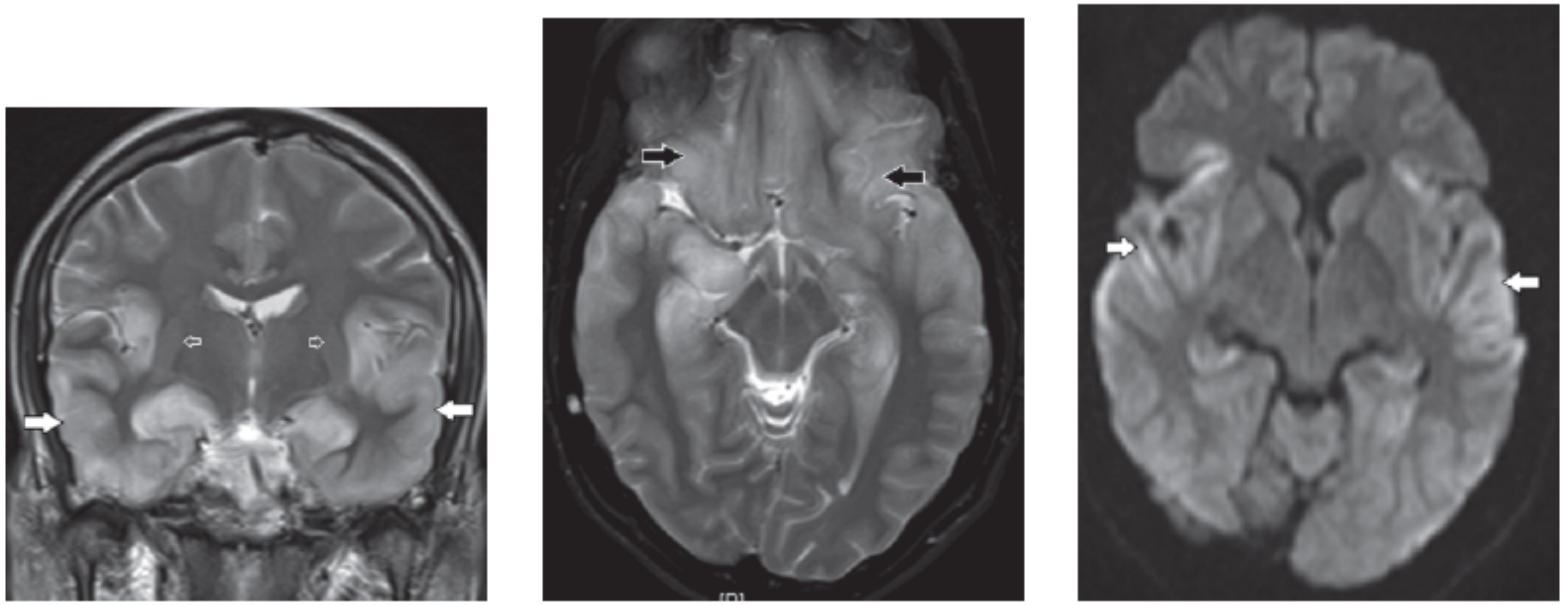
Clinico-radiological spectrum of bilateral temporal lobe hyperintensity: a retrospective review

J SUREKA, MD, FRCR and R K JAKKANI, MD, FRCR

n = 65

S. no.	Diagnosis	Clinical features	Bilateral temporal lobe hyperintensity			Additional MRI findings	Advanced MRI findings				Laboratory result
			Lobe	GM	WM		DWI	SWI	MRS	Gd-enhancement	
1	Herpes encephalitis	Fever, seizure, altered sensorium	A, M	+	–	Orbital gyri involvement, gyriform haemorrhages	R	+	ND	Gyriform	HSV antibodies in CSF
	temporal sclerosis	partial seizure				fornix and collateral WM atrophy					tion on EEG
3	Gliomatosis cerebri	Headache, recurrent seizures	A, M	+	+	Expansion of parenchyma, multilobar involvement	–	–	↑ML	Absent/patchy	Non-contributory
4	MELAS	Episodes of LOC, seizure	P, M	+	+	Fleeting hyperintensity, basal ganglia involvement	R	–	↑lac	Patchy	↑Serum and CSF lactate
5	Alzheimer's disease	Personality changes, memory loss	A, M	–	+	Hippocampal atrophy, enlarged parahippocampal fissures	–	–	↑ML	–	Non-contributory
6	MLC	Developmental delay, seizure	Whole	–	+	Temporal lobe cysts, subcortical WM, external capsule	–	–	↓NAA ↑cho	–	Non-contributory
7	Congenital CMV	Seizure	P	–	+	Periventricular cysts, pachygyria-agyria complex	–	–	ND	–	Non-contributory
8	CADASIL	Migraine, hemisensory loss	A, M	–	+	Lacunar infarcts, subcortical WM, external capsule and insula	–	–	ND	–	Non-contributory
9	Frontotemporal dementia	Dementia	A,M	–	+	Fronto-temporal atrophy	–	–	↓NAA ↑cho	–	Non-contributory
10	Limbic encephalitis	Memory disturbance	M	+	–	Cingulate gyrus, subfrontal cortex and inferior frontal WM	–	–	ND	–	Pleocytosis, lymphoma antibodies in CSF
11	Hyperammone-mia	Confusion, altered sensorium	A	+	–	Posterior cingulate gyrus	R	–	ND	ND	↑Blood ammonia
12	Wilson's disease	Weakness, extrapyra-midal symptoms	A, P, L	+	+	Fronto-parietal lobes, dorsal midbrain, deep grey nuclei	R	–	ND	–	↑Serum and urine copper, ↓ceruloplasmin
13	Myotonic dystrophy	Developmental delay, facial and distal limb weakness	A	–	+	Periventricular and deep WM, prominent VR spaces	–	–	ND	ND	Myotonic discharges in electromyography

↓, decreased; ↑, elevated; –, negative; +, positive; A, anterior; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; Cho, choline; CMV, cytomegalovirus; CPS, complex partial seizure; CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; EC, external capsule; EEG, electroencephalogram; Gd, gadolinium; GM, grey matter; HSV, herpes simplex virus; L, lateral; Lac, lactate; LOC, loss of consciousness; M, medial; MELAS, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes; ML, myoinositol; MLC, megalencephalic leukoencephalopathy with subcortical cysts; MRS, MR spectroscopy; NA, not applicable; NAA, *N*-acetylaspartate; ND, not done; P, posterior; R, restriction; S. no., serial number; SWI, susceptibility-weighted imaging; WM, white matter; VR, Virchow–Robin spaces.



(a) (b) (c)

Figure 1. A 34-year-old male with herpes encephalitis. (a) Coronal T_2 weighted image shows bilateral symmetric cortical swelling and hyperintensity involving the anteromedial temporal lobes including the insular cortex (white arrows) with characteristic sparing of basal ganglia (open arrows). (b) Axial T_2 weighted image shows additional involvement of orbital gyri (black arrows). (c) Axial diffusion-weighted image depicts restricted diffusion in the involved areas (white arrows).

Traitement URGENCE : ACICLOVIR iv

Prescription systématique de l'aciclovir devant toute suspicion de MEH sans attendre les résultats de la PCR

Facteur pronostique essentiel : précocité

Historique

- 1967 : Aciclovir
- Années 1990
- Nobel de médecine
  Georges Hitchings et Gertrude Elion (1988)

Skoldenberg B, and al. *Lancet 1984*
Powell KF and al. Lancet 1990
Rozenberg Fet al. J Clin Microbiol 1990

CAT pratique

- Aciclovir (Zovirax®) voie IV

  10 à 15 mg/kg toutes les 8 h
  (20 mg/kg chez l'enfant)
  Dilution perf 250 ml / 90 min
  14 à 21 jours (absence de consensus)

- Contrôle PCR herpès est-elle utile à J 14 ?
  PCR + : poursuite traitement ?
  PCR - : arrêt du traitement ?

  Tyler and al. Herpes. 2004
  Cinque and al. J Neurol Neurosurg 1996

- Risque d'insuffisance rénale ?
  dose-dépendante, régressive
  poursuivre le traitement en réduisant les doses de moitié et en hydratant d'avantage

- En cas de résistance (rare) : relais ganciclovir

Traitements associés ?

(hors anticonvulsivants)

Hypothèse:

Atteinte du SNC n'est pas seulement liée à l'activité cytopathogène du HSV mais également à la réponse immune de l'hôte (cytokines)

→ Corticothérapie : inhibition cytokines pro-inflammatoires

A systematic review on the role of adjunctive corticosteroids in herpes simplex virus encephalitis: is timing critical for safety and efficacy?

Ciro Ramos-Estebanez and al. Antivir Ther. 2013

RESULTS

"Data suggesting that steroids decrease the immunological response and enhance viral replication originated from non-neural microenvironments. Early steroid administration might be harmful for initial damage in HSVE that is mediated by viral replication. Steroid treatment improves outcomes in animal models by inhibiting the subsequent inflammatory response. Clinical observations support a similar benefit in symptomatic HSVE patients."

CONCLUSION

"Experimental and clinical observations suggest a benefit from adjunctive steroid therapy in HSVE. Nevertheless, current evidence is not yet sufficient to endorse this approach as a standard of practice"

Facteur(s) pronostique(s) MEH

Outcome of and Prognostic Factors for Herpes Simplex Encephalitis in Adult Patients: Results of a Multicenter Study

Table 3. Univariate analysis of factors associated with outcomes at 6 months for 85 patients with herpes simplex encephalitis.

Characteristic	Patients with favorable outcome (n = 55)	Patients with poor outcome (n = 30)	P
Age, mean years ± SD	50 ± 16.2	56.6 ± 16.8	.1
MacCabe score, mean ± SD	0.11 ± 0.4	0.1 ± 0.3	.92
Knaus score, mean ± SD	1.16 ± 0.4	1.43 ± 0.7	.04
GCS score, mean ± SD	13.7 ± 2.5	12.5 ± 3.4	.03
SAPS II, mean ± SD	27.6 ± 16.1	29.6 ± 12.1	.45
SAPS II >27, no. (%) of patients	9 (16)	17 (57)	.0001
Seizures, no. (%) of patients	18 (33)	9 (30)	.79
Focal neurological deficit, no. (%) of patients	11 (20)	9 (30)	.3
Serum sodium level, mean mM ± SD	132.4 ± 5.5	131.3 ± 5	.32
CSF parameters, mean ± SD			
Leukocyte count, cells/mL × 10^3	250 ± 546	170 ± 197	.39
Protein level, g/L	0.83 ± 0.6	0.78 ± 0.4	.39
Less than 2 days between hospital admission and initiation of acyclovir therapy, no. (%) of patients	41 (75)	9 (30)	.00008
Mechanical ventilation, no. (%) of patients	23 (42)	18 (60)	.97
Hospital-acquired infection, no. (%) of patients	17 (31)	20 (67)	.001

NOTE. GCS, Glasgow Coma Scale; SAPS, Simplified Acute Physiology Score.

Table 4. Multivariate analysis of factors associated with poor outcome at 6 months for 85 patients with herpes simplex encephalitis.

Parameter	OR (95% CI)	P
SAPS II >27 at hospital admission	3.7 (1.3–10.6)	.014
More than 2 days between hospital admission and initiation of acyclovir therapy	3.1 (1.1–9.1)	.037

NOTE. SAPS, Simplified Acute Physiology Score.

Raschilas et al. Clin Infect Dis. 2002

Autres avancées ?

N-Methyl-D-Aspartate Receptor Antibodies in Herpes Simplex Encephalitis

Harald Prüss, M.D.,[1] Carsten Finke, M.D.,[1] Markus Höltje, Ph.D.,[2] Joerg Hofmann, M.D.,[3] Christine Klingbeil,[4] Christian Probst, Ph.D.,[4] Kathrin Borowski,[4] Gudrun Ahnert-Hilger, Ph.D.,[2] Lutz Harms, M.D.,[1] Jan M. Schwab, M.D., Ph.D.,[1] Christoph J. Ploner, M.D.,[1] Lars Komorowski, Ph.D.,[4] Winfried Stoecker, M.D.,[4] Josep Dalmau, M.D., Ph.D.,[5,6] and Klaus-Peter Wandinger, M.D.[4,7]

Objective: To determine the presence and kinetics of antibodies against synaptic proteins in patients with herpes simplex virus encephalitis (HSE).
Methods: Retrospective analysis of 44 patients with polymerase chain reaction-proven HSE for the presence of a large panel of onconeuronal and synaptic receptor antibodies. The effect of patients' serum was studied in cultures of primary mouse hippocampal neurons.
Results: N-Methyl-D-aspartate receptor (NMDAR) antibodies of the immunoglobulin (Ig) subtypes IgA, IgG, or IgM were detected in 13 of 44 patients (30%) in the course of HSE, suggesting secondary autoimmune mechanisms. NMDAR antibodies were often present at hospital admission, but in some patients developed after the first week of HSE. Antibody-positive sera resulted in downregulation of synaptic marker proteins in hippocampal neurons.
Interpretation: Some patients with HSE develop IgA, IgG, or IgM autoantibodies against NMDAR. Sera from these patients alter the density of neuronal synaptic markers, suggesting a potential pathogenic disease-modifying effect. These findings have implications for the understanding of autoimmunity in infectious diseases, and prospective studies should reveal whether the subgroup of patients with HSE and NMDAR antibodies may benefit from immunotherapy.

ANN NEUROL 2012;72:902–911

Cas particulier : immunodépression

Table 1 Comparison of clinical characteristics of immunocompromised and immunocompetent groups

	Immunocompromised (n = 14)	Immunocompetent (n = 15)	*p* Value
Age, y, mean (SD)	56.2 (12.5)	54.1 (19.3)	0.73
Male, n (%)	6 (42.9)	8 (53.3)	0.57
Clinical characteristics			
Prodromal syndrome, n (%)	4 (28.6)	12 (80.0)	0.01
Fever, n (%)	11 (78.6)	12 (80.0)	0.92
Seizures, n (%)	7 (50.0)	10 (66.7)	0.36
Encephalopathy, n (%)	14 (93.3)	13 (92.8)	0.96
Focal deficits, n (%)	4 (28.6)	11 (73.3)	0.02
Delay presentation, d, mean (SD)	3.4 (3.7)	4.9 (3.8)	0.29
Delay acyclovir administration, d, mean (SD)	1.1 (1.7)	1.7 (1.9)	0.44
Completed 21-day acyclovir, n (%)	11 (78.6)	11 (73.3)	0.74
Total delay, d, mean (SD)	4.4 (4.7)	6.6 (4.3)	0.20
Transfer from other hospital, n (%)	4 (28.6)	9 (60.0)	0.09
Blood pleocytosis, cells/mm^3, mean (SD)	11.2 (12.4)	9.4 (5.50)	0.61
CSF findings, mean (SD)			
Pleocytosis, cell/mm^3	132.5 (191.9)	163.0 (205.7)	0.69
Protein, mg/dL	107.8 (70.5)	74.4 (47.9)	0.17
Glucose, mg/dL	60.7 (18.9)	70.3 (18.8)	0.21
Neuroimaging abnormalities, n (%)			
Unilateral temporal	11 (73.3)	8 (61.5)	0.51
Bilateral temporal	3 (23.1)	3 (20.0)	0.84
Others	8 (57.1)	8 (53.3)	0.84
Outcome			
Karnofsky Performance Status Scale, mean (SD)	39 (33)	61 (26)	0.046
Mortality, n (%)	5 (35.7)	1 (6.7)	0.054

Tan and al.
Neurology. 2012

Cas particulier : rechute

Case report

A case of late herpes simplex encephalitis relapse

Andrea Rigamonti[a,*], Giuseppe Lauria[b], Vittorio Mantero[a], Andrea Salmaggi[a]

[a] Department of Neurology, "Alessandro Manzoni" Hospital, Via Dell'Eremo 9/11, 23900 Lecco, Italy
[b] Neuromuscular Diseases Unit, "Carlo Besta" Neurological Institute, IRCCS Foundation via Celoria 11, 20133 Milan, Italy

15 cas de rechute "tardive" (80% chez enfant)
80% des cas dans l'année
Clinique : fièvre (10/15), crise convulsive (6/15)
Nouvelles lésions IRM 67% cas
Facteur déclenchant : immunodépression induite ?

Cas particulier : craniectomie ?

Craniectomy:

An aggressive treatment approach in severe encephalitis

S. Schwab, MD; E. Jünger, MD; M. Spranger, MD; A. Dörfler, MD; F. Albert, MD; H.H. Steiner, MD; and W. Hacke, MD

Article abstract—*Background and objective:* Focal encephalitis may be associated with brain edema, which is often fatal. The control of intracranial pressure (ICP) is therefore crucial for further therapeutic strategies in space-occupying edema following encephalitis. However, aggressive treatment strategies such as hemicraniectomy have not been described in a larger series of patients. *Patients and methods:* We describe the clinical course and outcome in six patients who developed severe brain edema associated with acute encephalitis. All received maximum medical treatment for elevated ICP, but with signs of brainstem compression emerging, hemicraniectomy was performed to control ICP. *Results:* All patients had a very severe encephalitic syndrome and were treated over the course of weeks in the neurocritical care unit (NCCU). However, all patients recovered almost completely and showed only mild or no neurologic deficit when reexamined after 4 months to 3 years. *Conclusion:* Hemicraniectomy should be considered in patients with severe brain edema following encephalitis as a potentially lifesaving therapeutic measure. Moreover, the initial neurologic deficit seems to have no impact on the long-term clinical outcome.

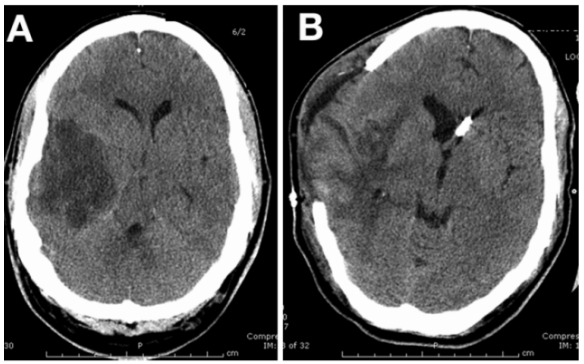
NEUROLOGY 1997;48:412–417

Emergency decompressive craniectomy for fulminating infectious encephalitis

*Summary of cases identified in the literature that underwent decompressive craniectomy for brainstem dysfunction due to fulminant infectious encephalitis**

Authors & Year	Age (yrs), Sex	Infectious Origin	Clinical Findings	CT Findings	Medical ICP Management Failed	Op	Long-Term Outcome (GOS Score)
Schwab et al., 1997	32, F	unknown	early: rt hemiparesis late: lt BFDP, ext	lt hemispheric edema	yes	lt C&D	short-term memory loss (4)
	29, F	unknown	early: rt hemiparesis late: BFDP, ext	lt hemispheric edema, midline shift	yes	lt C&D	mild rt hemiparesis (4)
	39, M	unknown	early: rt hemiparesis late: PERRL, no corneal reflex, flaccid	lt hemispheric edema	yes	lt C&D	(5)
	24, F	*Mycoplasma pneumoniae*	early: lt hemiparesis late: no lt corneal reflex, lt NDP, FP	rt temporoparietal lobe edema	yes	rt C&D	(5)
	25, M	HSV	presented comatose, FP	rt hemispheric edema	yes	rt C&D	(5)
	45, F	unknown	early: rt hemiparesis, global aphasia late: comatose	lt hemispheric edema	yes	lt C&D	(5)
Ebel et al., 1999	0.7, F	HSV	early: somnolence late: lt GTC, lt hemiparesis	lt temporal lobe, hemorrhagic conversion, uncal & transtentorial herniation	—	lt C + ATL	(5)
Taferner et al., 2001	42, M	HSV	early: headaches late: anisocoria, comatose	rt temporal lobe edema, hemorrhagic conversion	yes	rt C&D, evacuation of temporal lobe IPH	minor neurocognitive deficits (4)
	25, F	HSV	obtunded	rt frontotemporal lobe edema, transtentorial herniation	yes	rt C&D	completed university studies (5)
	28, M	*Mycoplasma pneumoniae*	FP	rt hemispheric edema, 10-mm midline shift & transtentorial herniation	yes	rt C&D	mild lt hemiparesis, resumed work as a car salesman (4)
	17, M	unknown	CN III palsy, comatose, tetraparesis	diffuse bilat brain edema, hemorrhagic conversion, transtentorial herniation	yes	bilat C&D	no cognitive deficits; permanent paraplegia required him to get a different job (4)
Yan 2002	48, F	HSV	early: severe HA late: rt hemiparesis, anisocoria	lt temporal lobe edema, hemorrhagic conversion	—	lt C&D + ATL	postop stutter (4–5)
	37, F	HSV	early: HA, memory loss, personality change late: anisocoria, GCS score dec (14–9)	lt temporal lobe edema, hemorrhagic conversion, & brainstem compression	—	lt C&D + ATL	(5)

* ATL = anterior temporal lobectomy; BFDP = bilaterally fixed and dilated pupils; CN = cranial nerve; C&D = craniectomy and duraplasty; dec = decrease; early = symptoms and neurological examination at presentation; ext = extensor decerebrate posturing; FP = flexion posturing on neurological examination; GCS = Glasgow Coma Scale; GTC = generalized tonic–clonic seizure; HA = headache; IPH = intraparenchymal hemorrhage; late = delayed symptoms and neurological examination; NDP = nonreactive dilated pupil; PERRL = pupils equal round reactive to light; — = not discussed.



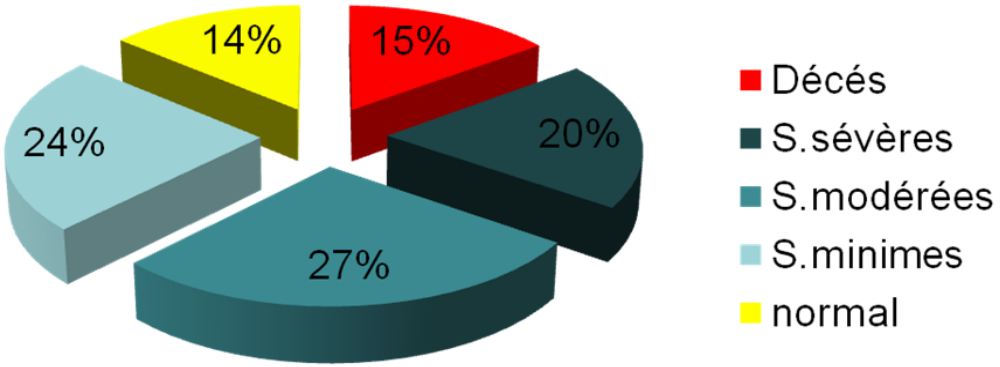
Score GOS : Glasgow outcome scale

Score	Détail
1	Décés
2	**Etat végétatif persistant** (Absence d'activité corticale)
3	**Handicap sévère** (Conscient mais dépendant : atteinte mentale ou motrice ou les deux)
4	**Handicap modéré**. Patient cependant autonome dans la vie quotidienne (dysphasie, hémiparésie, ataxie, troubles intellectuels ou de mémoire, troubles de la personnalité)
5	**Bonne récupération** Activités normales (déficits neurologiques ou psychologiques mineurs)

M A. Adamo and al.
J. Neurosurg. 2008

MHE : Séquelles

L'instauration des antiviraux n'a pas supprimé les séquelles



Raschilas et al. 2002

25% des survivants

Réhospitalisés

pour crise convulsive

Herpes Simplex Encephalitis in Sweden, 1990–2001: Incidence, Morbidity, and Mortality

Anders Hjalmarsson,[1] Paul Blomqvist,[2] and Birgit Sköldenberg[1]

[1]Infectious Diseases Unit and [2]Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

(See the editorial commentary by Whitley and Gnann on pages 881–2)

Background. Herpes simplex encephalitis (HSE) is a devastating disease.

Methods. In Sweden, a nationwide retrospective study of the incidence, morbidity, and mortality associated with HSE during the 12-year period 1990–2001 was conducted. The national inpatient register data were used, and diagnostic data from the virus laboratories were validated.

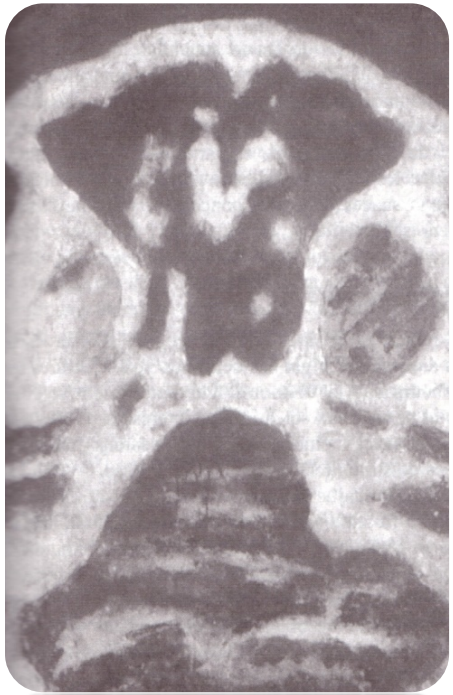
Results. In the study period, 638 patients hospitalized in Sweden received a primary diagnosis of HSE. Of these, 236 patients had a confirmed infection of the central nervous system due to herpes simplex virus type 1. This corresponds to an incidence of confirmed HSE due to herpes simplex virus type 1 of 2.2 cases per million population per year. Of the survivors, 87% were readmitted to the hospital. The most frequent diagnosis at readmission was epilepsy, which was found in 49 patients (21% of the 236 total patients; 24% of 203 survivors), with a median onset 9.3 months after the diagnosis of HSE. This corresponds to a 60- to 90-fold increase in risk, compared with that for the general population. Neuropsychiatric sequelae were evident in 45 (22%) of 203 surviving patients. The incidence of venous thromboembolism, including pulmonary embolism, was 5–14 times higher than that in the general population. Among patients with HSE due to herpes simplex virus type 1, the 1-year mortality was 14% (33 of 236 patients died), which was 8 times higher than expected.

Conclusions. This is, to our knowledge, the first study to report long-term, nationwide follow-up data for patients with virologically confirmed HSE. There is considerable morbidity after HSE, with epilepsy being the most common diagnosis. This demonstrates the need for expanding our knowledge of the pathogenesis of HSE to direct more effective antiviral and antiinflammatory treatments.

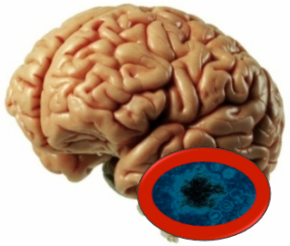
- **Épilepsie séquellaire (lésionnelle)**

- **Séquelles mnésiques**
  - syndrome amnésique pur de type Korsakoff
  - trouble de l'apprentissage épisodique
  - préservation de la mémoire à court terme et rétrograde

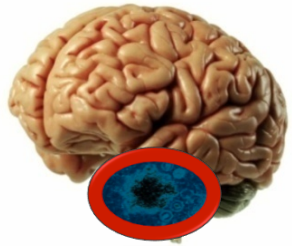
- **Séquelles comportementales**
  - syndrome de Kluver et Bucy
  - troubles anxiodépressifs
  - hyperémotivité et irritabilité



Reaffirmation II
David Jane



ENCÉPHALITE HERPÉTIQUE



SYNTHÈSE

MEH : 20% encéphalites sporadiques

Elément de décision thérapeutique primordial : diagnostic d'encéphalite !

Tout trouble du comportement fébrile doit faire redouter une MEH

Diagnostic : PCR HSV (LCR) / IRM cérébrale

MEH est curable +++ : Aciclovir IV dès diagnostic suspecté (14 à 21 jours)

Facteur pronostic : délai début traitement

Incertitudes ?

Encéphalite herpétique

2 000 ans d'histoire

Une seule certitude

« Toute suspicion de MEH doit faire débuter en urgence un traitement antiviral par aciclovir »