Encéphalites

Romain Sonneville

Médecine Intensive - Réanimation

APHP, Hôpital Bichat Claude Bernard, Paris

Université de Paris, INSERM UMR1148

romain.sonneville@aphp.fr

@romsonnevil

Université de Paris

LVTS Laboratory for Vascular Translational Science

AP-HP. Nord Université de Paris

Encephalitica

Conflicts of interest

RS received grants from the French Ministry of Health.

Encéphalites aiguës

De quoi parle-t-on ?

Epidémiologie et pronostic

Prise en charge initiale

Causes principales justifiant un traitement spécifique

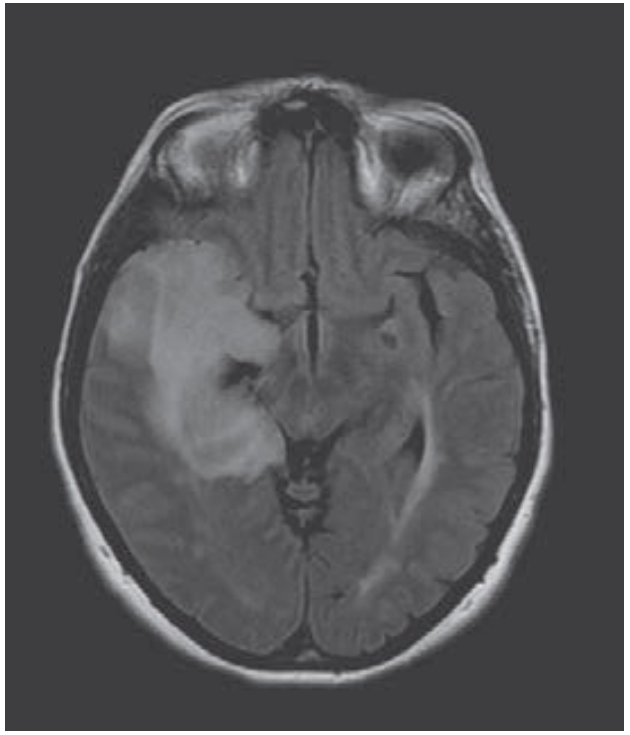
Mesures symptomatiques

Pronostic à long terme

Conclusion

Encephalitis

Inflammation	Brain parenchyma
Causes	Viral Immune-mediated
Altered mental status	+
Fever	+
Meningism	+/-
Focal signs	+/-
Seizures	+/-



Case Definitions, Diagnostic Algorithms, and Priorities in Encephalitis: Consensus Statement of the International Encephalitis Consortium

- MAJOR CRITERION : altered mental status lasting ≥24 h

(altered level of consciousness, lethargy or personality change)

- MINOR CRITERIA (at least 3 for probable or confirmed encephalitis)
  - Fever >38° C (within 72H before or after presentation)
  - New-onset seizures
  - Focal sign(s)
  - CSF pleocytosis : ≥ 5 cell/mm^3
  - Brain imaging findings consistent with encephalitis
  - EEG alterations compatible with encephalitis

A. Venkatesan, Clin Infect Dis 2013

Case Definitions, Diagnostic Algorithms, and Priorities in Encephalitis: Consensus Statement of the International Encephalitis Consortium

CONFIRMED encephalitis

If there is…

- evidence of **acute CNS infection** with a microorganism associated with encephalitis **(CSF PCR)**

OR

- laboratory evidence of an **autoimmune condition** associated with encephalitis **(Antibody testing in blood and CSF)**

OR

- **pathologic confirmation** of brain inflammation (brain biopsy)

A. Venkatesan, Clin Infect Dis 2013

REVIEW ARTICLE

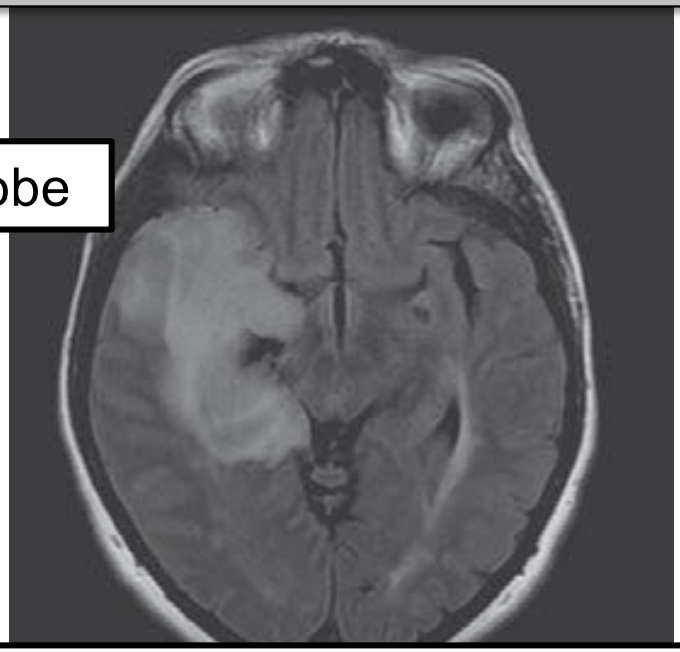
Allan H. Ropper, M.D., *Editor*

Acute Viral Encephalitis

Kenneth L. Tyler, M.D.

Many causes…

The most commonly identified causes are **neurotropic viruses**.



Herpes simplex encephalitis

New Eng J Med 2018

Encéphalites aiguës

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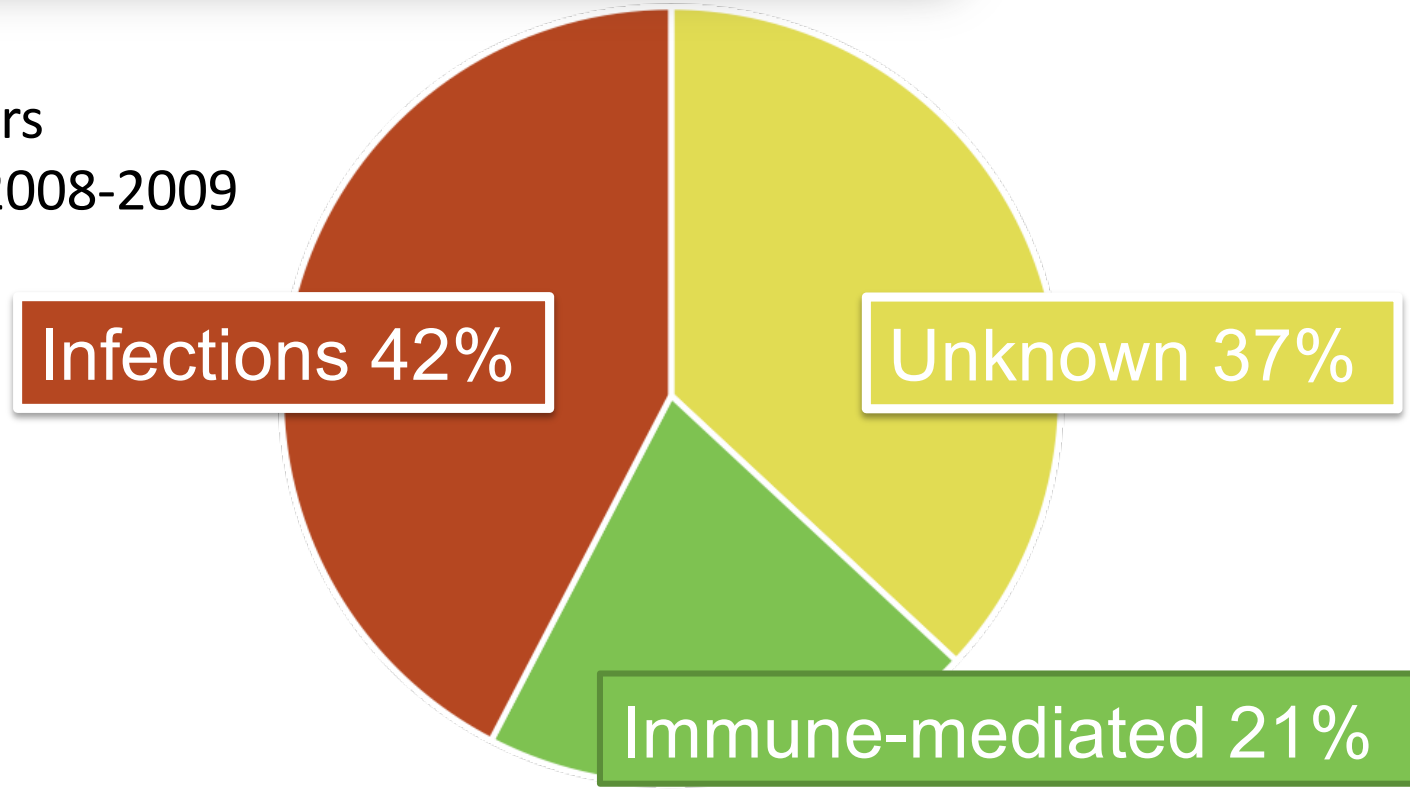
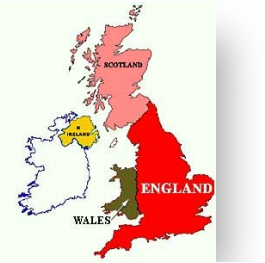
Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study

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

203 patients
Adults > 16 yrs
18 months, 2008-2009





J Granerod, Lancet Infectious Diseases 2010

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

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203 patients
Adults > 16 yrs
18 months, 2008-2009

	Immunocompetent patients* (n=172)
Herpes simplex virus	37 (22%, 16–28)
Acute disseminated encephalomyelitis	23 (14%, 9–19)
Antibody-associated encephalitis	15 (9%, 5–14)
Mycobacterium tuberculosis	9 (5%, 2–10)
Varicella zoster virus	4 (2%, 0·6–6)
Streptococci	4 (2%, 0·6–6)
Enterovirus	3 (2%, 0·4–5)

J Granerod, Lancet Infectious Diseases 2010

A Prospective Cohort Study to Identify Clinical, Biological, and Imaging Features That Predict the Etiology of Acute Encephalitis

Marion Le Maréchal,[1,2] Alexandra Mailles,[2,3] Arnaud Seigneurin,[4,5] Pierre Tattevin,[2,6,©] Jean-Paul Stahl,[1,2] and Olivier Épaulard[1,2,7]; on behalf of the Scientific Committee and Investigators Group

Table 2. Etiologic Pathogens in the National Cohort of Infectious Encephalitis in France Cohort: 31 July 2018

Pathogen	N = 349	Proportion of the Whole Cohort (%)	Proportion Among Encephalitis With Documented Etiology (%) N = 232
Herpes simplex virus	88[a]	25.2	37.9
Varicella-zoster virus	39	11.2	16.8
Tick-borne encephalitis virus	22	6.3	9.5
Listeria monocytogenes	19	5.4	8.2
Influenza virus	11	3.2	4.7
Mycobacterium tuberculosis	8	2.3	3.4
Epstein-Barr virus	6	1.7	2.6
Measles virus	4	1.1	1.7
Borrelia spp., JC virus, West Nile virus	3	0.9	1.3
Cryptococcus spp., enterovirus, human herpes virus-6, Japanese encephalitis virus, *Leptospira* spp., *Mycoplasma pneumoniae*	2	0.6	0.9
Bartonella spp., *Capnocytophaga canimorsus*, chikungunya virus, cytomegalovirus, *Coxiella burnetii*, human immunodeficiency virus, human coxsackie virus, *Legionella* spp., *Rickettsia* spp., Toscana virus, *Treponema pallidum*, *Tropheryma whipplei*, Zika virus	1	0.3	0.4
Unknown	117	33.5	-

Abbreviations: JC virus, John Cunningham virus; (-) dash, no analysis realized.
[a]Herpes simplex virus (HSV) 1, 73 HSV1, 6 HSV2, 8 undetermined HSV.

Clin Inf Diseases 2020

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Beyond Viruses: Clinical Profiles and Etiologies Associated with Encephalitis

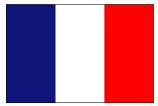
C. A. Glaser,[1] S. Honarmand,[1] L. J. Anderson,[3] D. P. Schnurr,[1] B. Forghani,[1] C. K. Cossen,[1] F. L. Schuster,[1] L. J. Christie,[1] and J. H. Tureen[2]

1998-2005: 1570 patients (adults and children)

ICU admission 58%

Clin Infect Dis, 2006

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

2007: 253 patients (adults)

ICU admission 46%

Clin Infect Dis 2009

Disponible en ligne sur ScienceDirect www.sciencedirect.com
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Médecine et maladies infectieuses
Médecine et maladies infectieuses 47 (2017) 179–194

Recommendations/Recommandations

Guidelines on the management of infectious encephalitis in adults

Recommandations de prise en charge des encéphalites infectieuses de l'adulte

J.P. Stahl [a,*,1], P. Azouvi [b], F. Bruneel [c], T. De Broucker [d], X. Duval [e], B. Fantin [f], N. Girard [g], J.L. Herrmann [h], J. Honnorat [i], M. Lecuit [j,k], A. Mailles [l,1], L. Martinez-Almoyna [m], P. Morand [n], L. Piroth [o], P. Tattevin [p,1], The reviewing group[2]

***Recommandations* SPILF 2017**

Grade B : Hospitalisation initiale en USC – réanimation

- **GCS < ou = 13** ou agitation
- **Crise(s) convulsive(s)**
- **Défaillance(s) extra-neurologique(s)**

Case Definitions, Diagnostic Algorithms, and Priorities in Encephalitis: Consensus Statement of the International Encephalitis Consortium

Epidemiological data

Medical history
Immunosuppression
Medications
Seasonal/epidemic context ?
Recent travel ?
Contacts:
- animals
- Insects

Recent immunization

Clinical findings

Neurological signs
Optic nerve
Extra-neurological signs

Other exams

BRAIN MRI with gd
CSF (cultures, PCR)
EEG
Serologies
Immunology tests

+/- brain biopsy ? ?

A. Venkatesan, Clin Infect Dis 2013

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***Recommandations* SPILF 2017**

Grade A : en l'absence d'orientation étiologique, **le traitement initial** associe :

Aciclovir : 10mg/kg/8h IVL (dans les 6h suivant admission)

ET

Amoxicilline : 200 mg/kg/24h IVL en perfusion continue

Adapter les posologies à la fonction rénale

Réévaluer à 48 heures +++

(cultures bactériennes, PCR HSV, VZV, enterovirus)

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

Franck Raschilas,[1,2] Michel Wolff,[2] Frédérique Delatour,[3] Cendrine Chaffaut,[4] Thomas De Broucker,[5] Sylvie Chevret,[4] Pierre Lebon,[1] Philippe Canton,[6] and Flore Rozenberg,[1] for the French Herpes Simplex Encephalitis Study Group[a]

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

This study suggests that **rapid diagnosis and early administration of antiviral treatment** are keys to a **favorable outcome.**

Clin Inf Dis 2002

Disponible en ligne sur ScienceDirect www.sciencedirect.com
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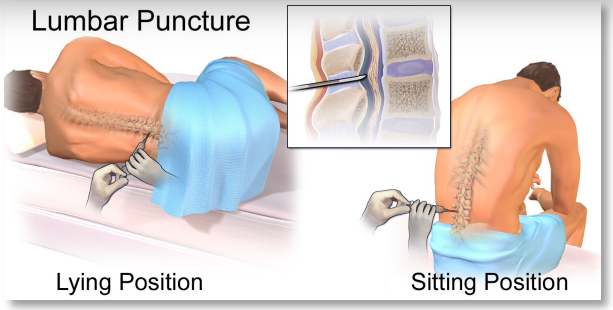

***Recommandations* SPILF 2017**

Grade A : la quantité de LCS à prélever doit être d'au moins 120 gouttes

(1ml =20 gouttes)

1ml pour biochimie

5 ml pour microbiologie (bactériologie +/- BK, virologie, mycologie….)

Conserver LCS à +4°C puis à -80°C si possible

**** CSF Interpretation					
Investigation	**Normal**	**Bacterial**	**Viral**	**Tuberculous**	**Fungal**
Opening pressure	10-20cm	Highly Cloudy	Normal/high	High	High/very high
Colour	Clear	Cloudy	"Gin" clear	Cloudy/yellow	Clear/cloudy
Cells	<5	High/very high 100-50000	Slightly increased 5-1000	Slightly increased <500	Normal-high 0-1000
Differential	Lymphocytes	Neutrophilis	Lymphocytes	Lymphocytes	Lymphocytes
CSF/Plasma Glucose	50-66%	Low<40%	Normal	Low-very low (30%)	Normal-low
Protein (g/l)	<0.45	High >1	Normal-high 0.5-1	High-very high 1.0-5.0	Normal-high 0.2-5.0

T. Solomon, UK guidelines for management of encephalitis, 2012

Case Definitions, Diagnostic Algorithms, and Priorities in Encephalitis: Consensus Statement of the International Encephalitis Consortium

Routine studies
CSF (unless contraindicated[b])
Opening pressure, leukocyte count with differential, erythrocyte count, protein, glucose
Gram stain and bacterial culture
HSV-1/2 PCR (if test available, consider HSV CSF IgG and IgM in addition)
VZV PCR (sensitivity may be low; if test available, consider VZV CSF IgG and IgM in addition)
Enterovirus PCR
Cryptococcal antigen or India ink staining

Immunodepression ?

PCR CMV, HHV6
PCR HIV, JC virus
PCR *Toxoplasma gondii*
M. Tuberculosis
Fungal infections

A. Venkatesan, Clin Infect Dis 2013

Bilan « 1ère ligne » en l'absence d'orientation étiologique évidente ….

Table 3. Initial and Subsequent Virologic Evaluation for Encephalitis According to Immune Status.*

Tier	Virologic Testing				Comments
	CSF PCR and RT-PCR Tests	CSF Serologic Tests	Serum Serologic Tests	Other Tests	
Immunocompetent patients					
Tier 1 (initial testing)	HSV-1, HSV-2	—	—	—	
	VZV	VZV IgM			
	Enterovirus	—	—	Nasopharyngeal and stool RT-PCR for enterovirus	
	HPeV	—	—	—	In children <3 yr old
	—	WNV, arbovirus IgM	WNV, arbovirus IgG, IgM	—	Arbovirus testing based on geographic region and season†
Immunocompromised patients					
Tier 1 (in addition to tier 1 above)	CMV	—	—	Serum CMV viral load	
	HHV-6, HHV-7	—	HHV-6, HHV-7	—	
	JC virus	—	JC virus	—	
	LCMV	LCMV	LCMV		
	WNV	—	—	—	Arbovirus testing based on geographic region and season†
Tier 2 (in addition to tier 2 above)	—	—	—	NGS	

New Eng J Med 2018

Bilan « 2ème ligne et 3ème ligne …. »

Table 3. Initial and Subsequent Virologic Evaluation for Encephalitis According to Immune Status.*

Tier	Virologic Testing				Comments
	CSF PCR and RT-PCR Tests	CSF Serologic Tests	Serum Serologic Tests	Other Tests	
Tier 2	HIV	—	HIV	HIV viral load	
	Adenovirus	—	—	Nasopharyngeal PCR for adenovirus	In children
	EBV	—	EBV	—	
	Measles virus	Measles virus	Measles virus	Nasopharyngeal and urine RT-PCR for measles virus	In unvaccinated patients
	Mumps virus	Mumps virus	Mumps virus	Salivary PCR for mumps virus	In unvaccinated patients
	—	—	—	Nasopharyngeal PCR for influenza A or B virus	
	—	—	—	Stool RT-PCR for rotavirus	In children
	HHV-6, HHV-7	—	HHV-6, HHV-7	—	In patients <30 yr old
	B19	—	B19	—	
Tier 3	—	—	—	NGS	

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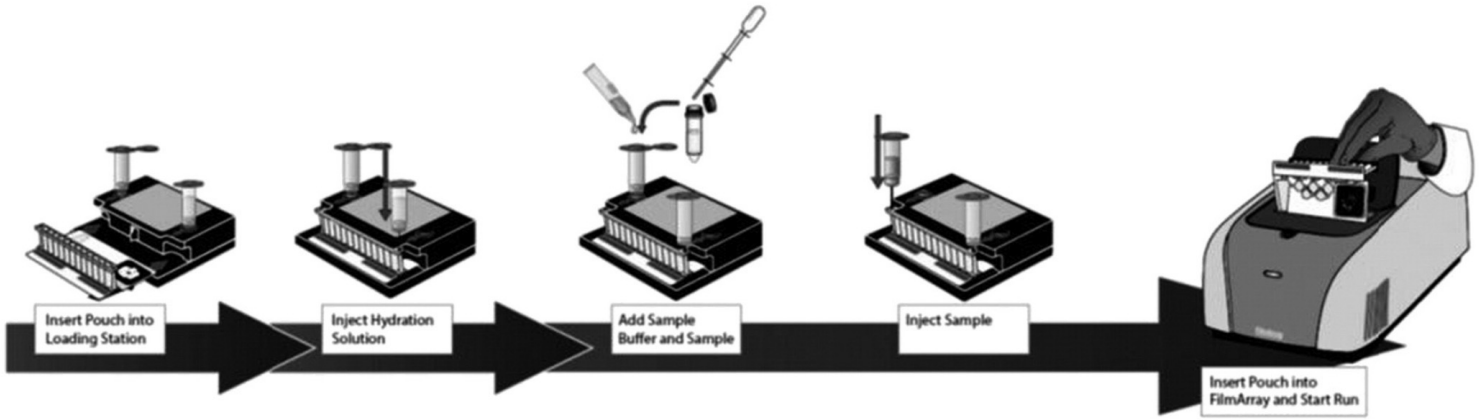
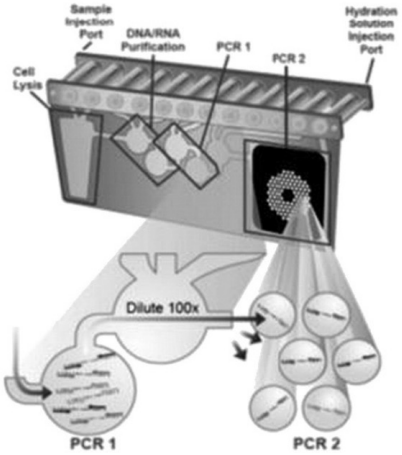
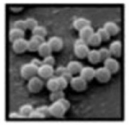
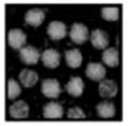






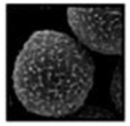
Bacteria

Escherichia coli
Haemophilus influenzae
Listeria monocytogenes
Neisseria meningitidis
Pseudomonas aeruginosa
Staphylococcus aureus
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)
Parechovirus
Varicella-zoster virus (VZV)



Fungus

Cryptococcus neoformans/gattii

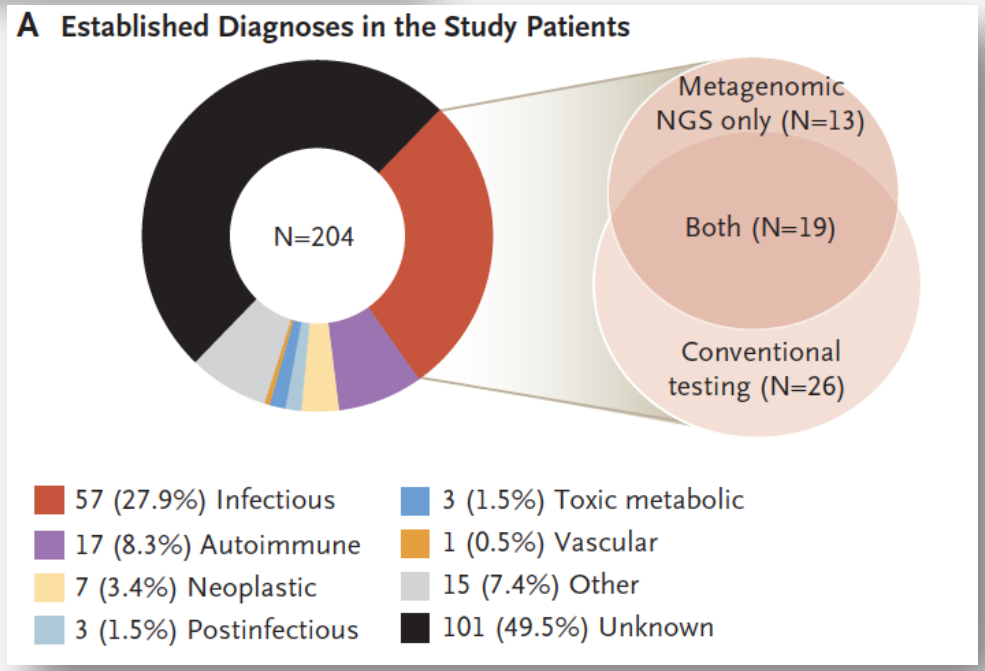
14 pathogens
in 1 hour !

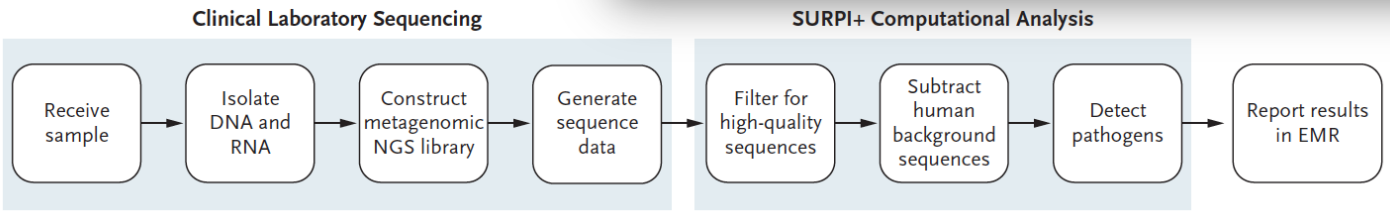
Fig. 1. The FilmArray multiplex PCR system.

J. Rhein, Diagn Microbiol Infect Dis 2015

ORIGINAL ARTICLE

Clinical Metagenomic Sequencing for Diagnosis of Meningitis and Encephalitis





New Eng J Med 2018

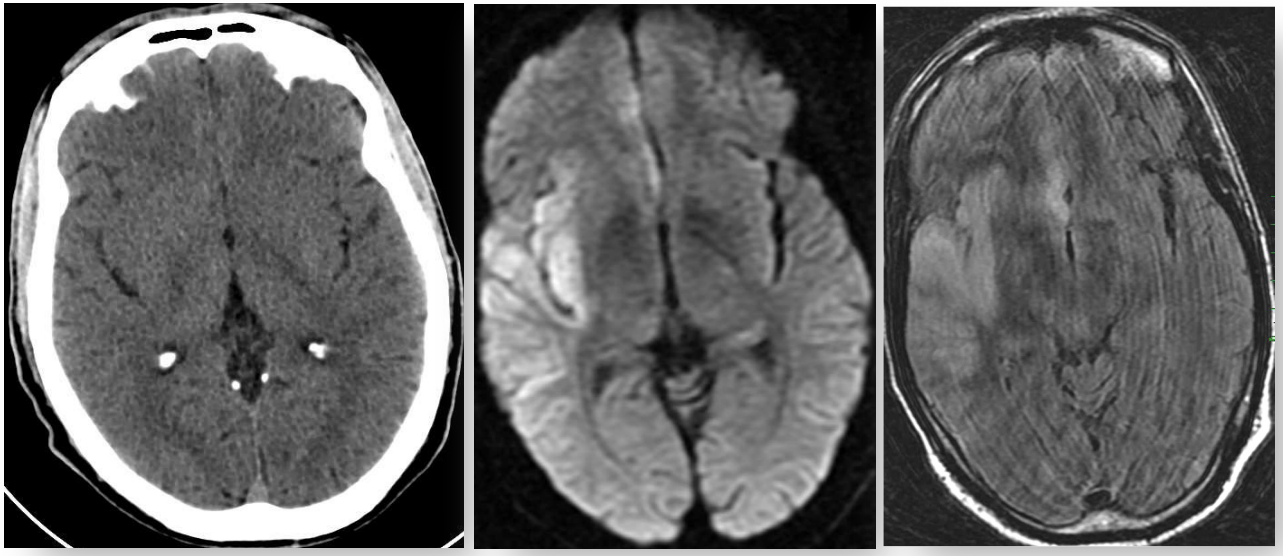
***Recommandations* SPILF 2017**

Grade A : si elle est possible, **l'IRM cérébrale** est l'imagerie à réaliser **en première intention (Diffusion, FLAIR, T2*, T1 gadolinium)**

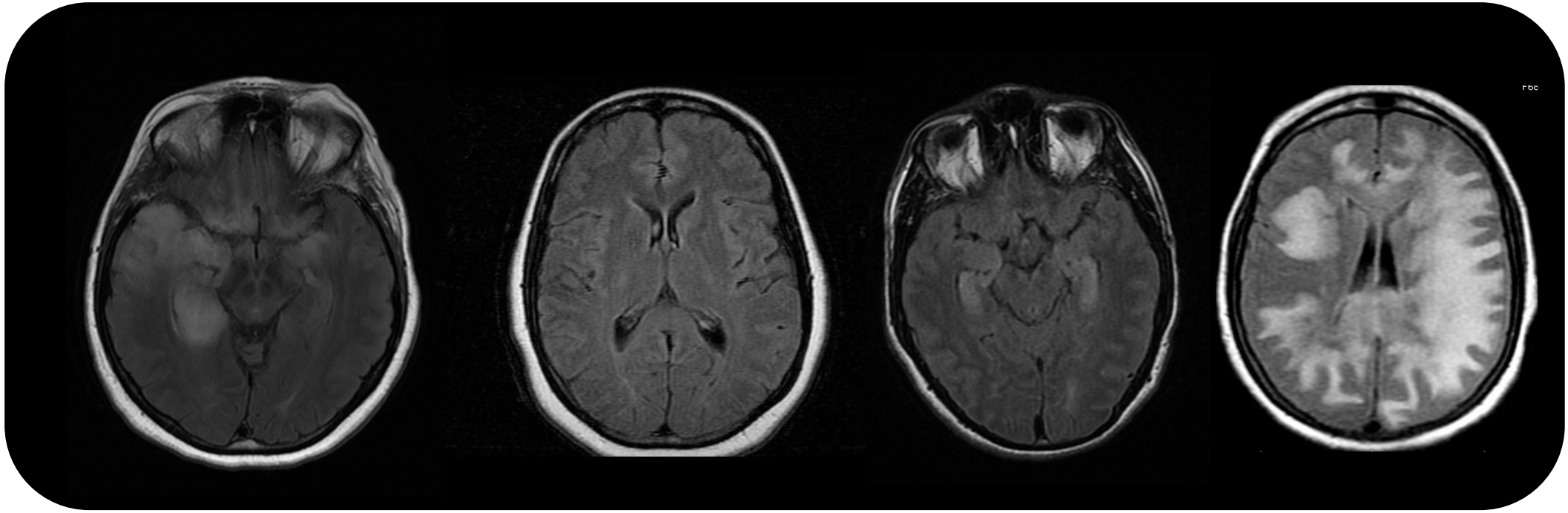
H 27 ans, confusion, Fièvre 38.7° C

PL : 80 éléments / mm^3, 90% lymphocytes, prot 0.8g/l, glycorachie 4 mmol/l

Aciclovir IV 10mg/kg/8h IVL



Brain MRI patterns



« Grey »

Normal

« Limbic »

« Demyelination »

IMMUNE-MEDIATED ?

R. Sonneville et al., Revue Neuroi 2022

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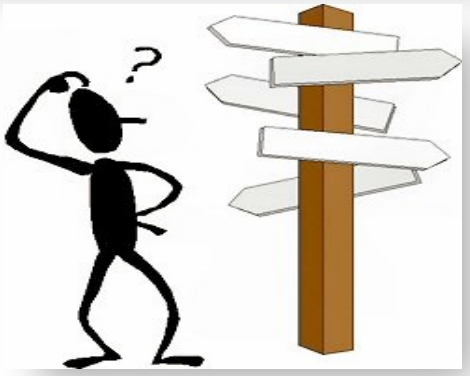
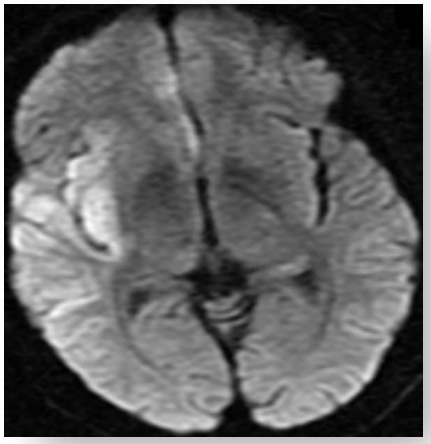
EASILY MISSED?

Herpes simplex encephalitis

Why is it missed?

- Signes frustres chez ID et sujets agés
- Absence de fièvre : 10-15%
- LCS acellulaire : 10-15%
- TDM initial normal : 33%
- IRM initiale normale : <10%
- PCR HSV négative au début des symptômes





M Sabah, BMJ 2012

ONLINE BRIEF REPORT

Herpes Simplex Virus Encephalitis With Initial Negative Polymerase Chain Reaction in the Cerebrospinal Fluid: Prevalence, Associated Factors, and Clinical Impact

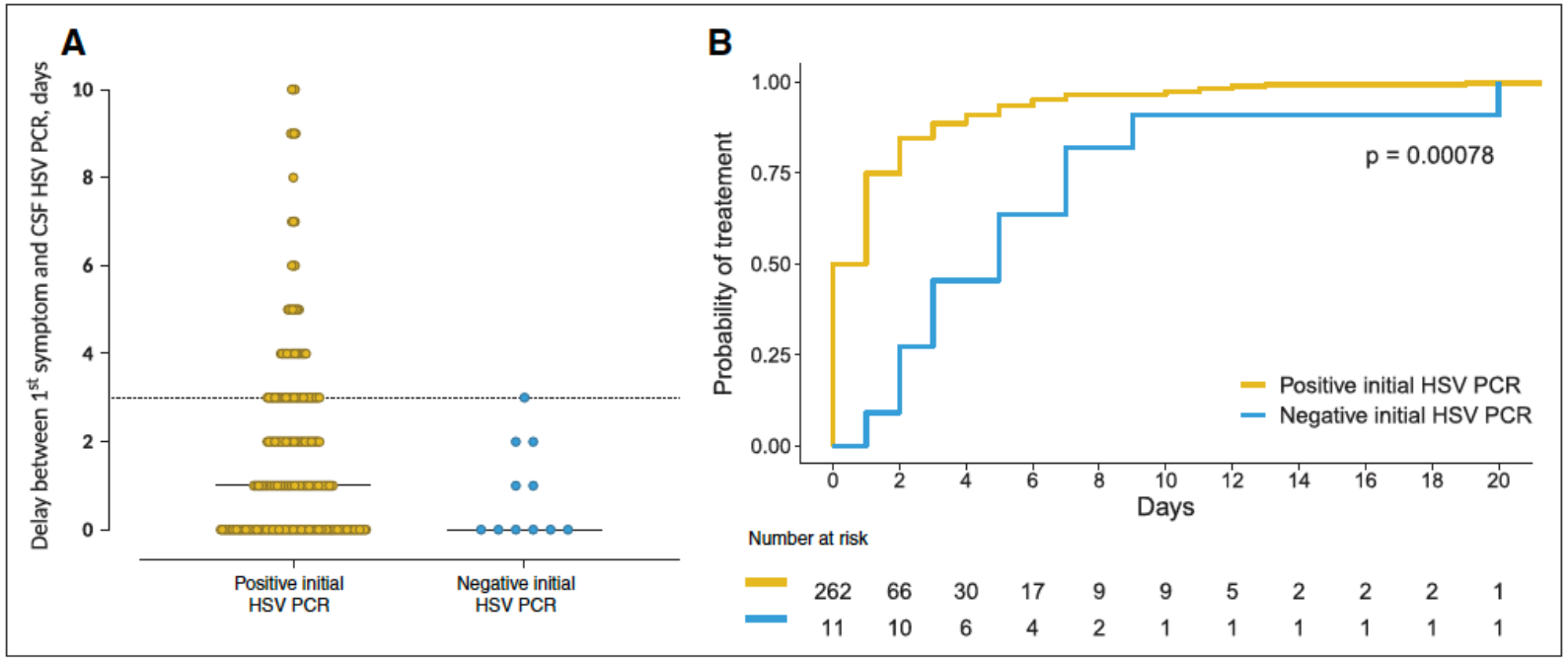


Figure 1. A, Delay from first symptom onset to lumbar puncture according to herpes simplex virus (HSV) polymerase chain reaction (PCR) positivity in initial cerebrospinal fluid (CSF) testing. **B**, Probability of acyclovir treatment from hospital admission, according to initial HSV PCR results. *p* value is based on log-rank test.

E. de Montmollin et al., Crit Care Med 2022

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Acyclovir for viral encephalitis

- **HSV-1 / HSV-2**

Acyclovir IV : 10 mg/kg/8h IVL (normal renal function)

Duration ACV : **14 days (21 days if immunocompromised)**

- **VZV**

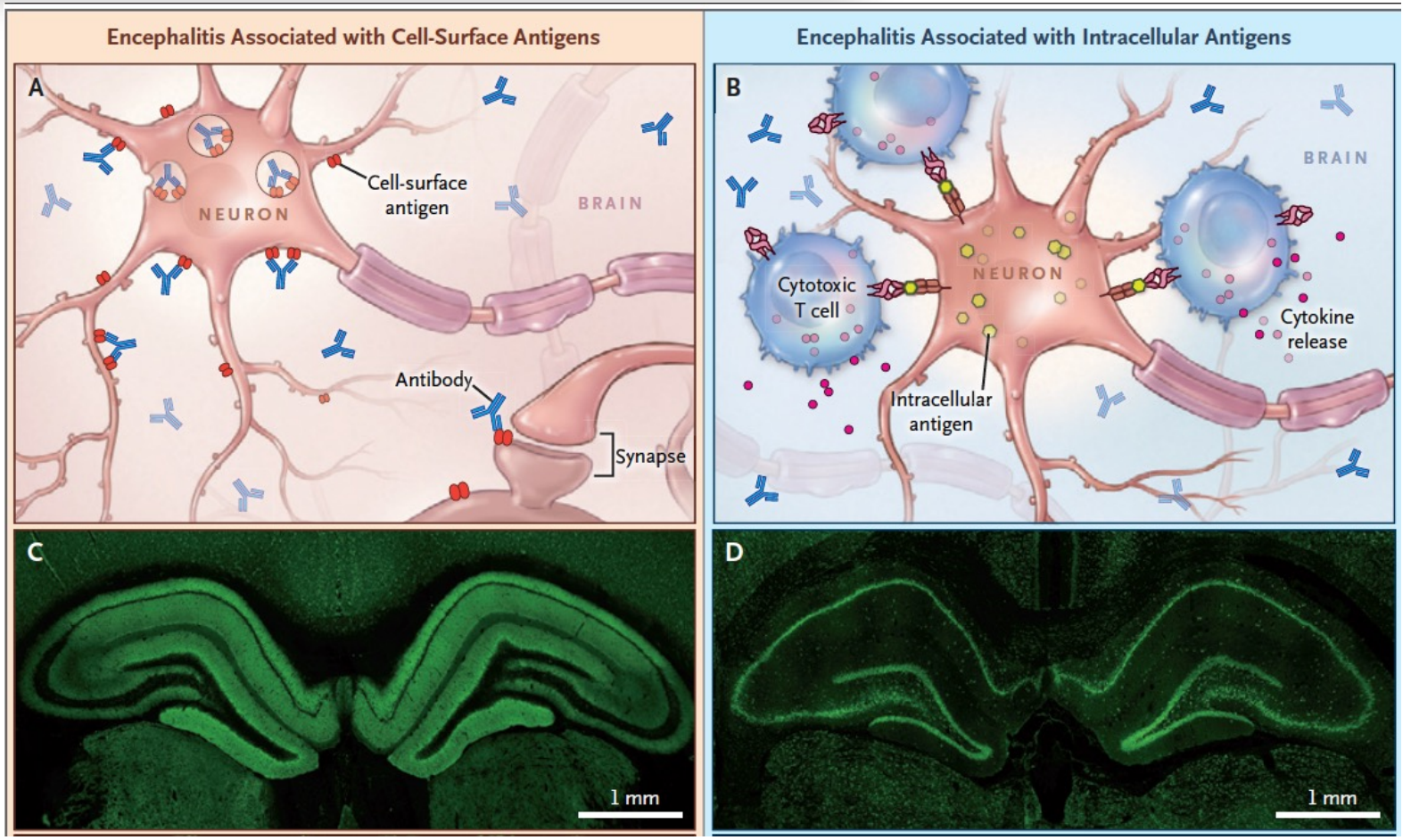
Acyclovir IV : 15 mg/kg/8h IVL (normal renal function)

Duration ACV : **21 days**

Adjunctive steroids if evidence of vasculitis

Antibody-Mediated Encephalitis

Josep Dalmau, M.D., Ph.D., and Francesc Graus, M.D., Ph.D.



New Eng J Med 2018

Neuro-inflammation

OPEN ACCESS

Review

Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management

Hesham Abboud ,[1,2] John C Probasco,[3] Sarosh Irani ,[4] Beau Ances,[5] David R Benavides,[6] Michael Bradshaw,[7,8] Paulo Pereira Christo,[9] Russell C Dale,[10] Mireya Fernandez-Fournier,[11] Eoin P Flanagan ,[12] Avi Gadoth,[13] Pravin George,[14] Elena Grebenciucova,[15] Adham Jammoul,[14] Soon-Tae Lee,[16] Yuebing Li,[14] Marcelo Matiello,[17,18] Anne Marie Morse,[19] Alexander Rae-Grant,[14] Galeno Rojas,[20,21] Ian Rossman,[22] Sarah Schmitt,[23] Arun Venkatesan,[3] Steven Vernino,[24] Sean J Pittock ,[12] Maarten J Titulaer ,[25] Autoimmune Encephalitis Alliance Clinicians Network

Box 1 Best practice recommendations summary for acute management of autoimmune encephalitis (AE)

1. Evaluate the likelihood of AE relative to the patient's clinical picture.
2. Perform brain MRI and/or EEG to look for focal or multifocal brain abnormality.
3. Perform lumbar puncture to support inflammatory aetiology and rule out infective/neoplastic causes. Test oligoclonal bands, IgG index, IgG synthesis rate and neuronal autoantibodies in the cerebrospinal fluid (CSF).
4. Send blood tests to rule out other potential causes guided by neuroanatomical and clinical data. Test neuronal autoantibodies in the serum.
5. Consider brain FDG-PET when there is a high clinical suspicion of AE and other paraclinical studies are uninformative.
6. Perform cancer screening with CT chest, abdomen, and pelvis with contrast in relevant cases (or MRI when CT is contraindicated or not preferred). If negative, consider further testing with mammogram/breast MRI, pelvic ultrasound, and/or whole body FDG-PET guided by the clinical presentation and each patient's specific cancer risk factors.

J Neurol Neurosurg Psychiatry 2021

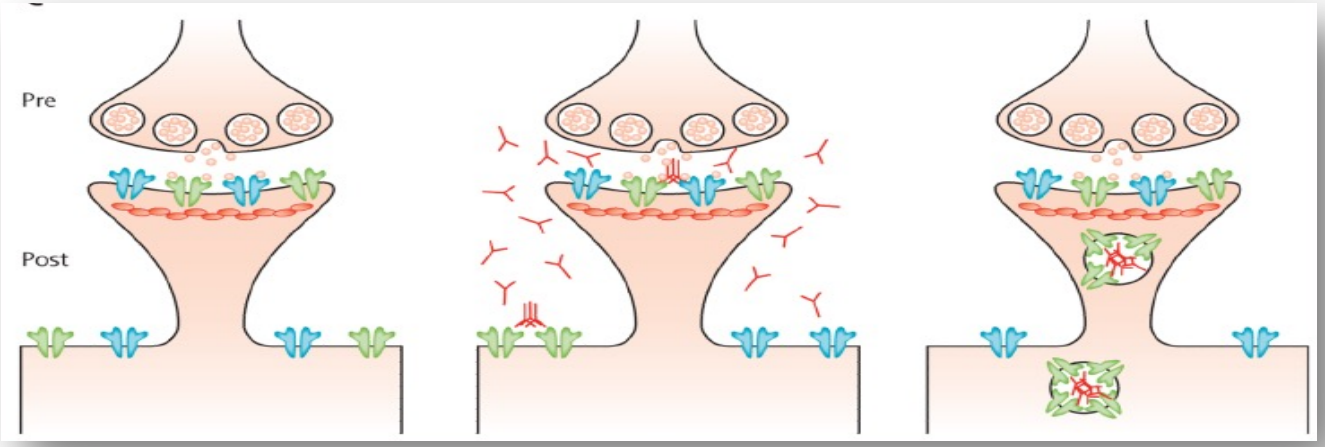
A clinical approach to diagnosis of autoimmune encephalitis

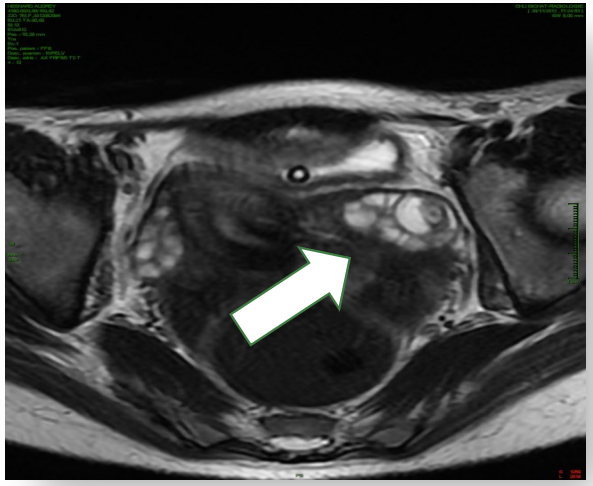
Francesc Graus, Maarten J Titulaer, Ramani Balu, Susanne Benseler, Christian G Bien, Tania Cellucci, Irene Cortese, Russell C Dale, Jeffrey M Gelfand, Michael Geschwind, Carol A Glaser, Jerome Honnorat, Romana Höftberger, Takahiro Iizuka, Sarosh R Irani, Eric Lancaster, Frank Leypoldt, Harald Prüss, Alexander Rae-Grant, Markus Reindl, Myrna R Rosenfeld, Kevin Rostásy, Albert Saiz, Arun Venkatesan, Angela Vincent, Klaus-Peter Wandinger, Patrick Waters, Josep Dalmau

	Syndrome	Diagnostic assay	Frequency of cancer	Main type of cancer
Antibodies against intracellular antigens				
Hu (ANNA1)[8]*	Limbic encephalitis	Western blot	>95%	Small-cell lung carcinoma
Ma2[9]	Limbic encephalitis†	Western blot	>95%	Testicular seminoma
GAD[10]	Limbic encephalitis‡	Radioimmunoassay	25%§	Thymoma, small-cell lung carcinoma
Antibodies against synaptic receptors				
NMDA receptor[11]	Anti-NMDA receptor encephalitis	Cell-based assay	Varies with age and sex	Ovarian teratoma¶
AMPA receptor[12]	Limbic encephalitis	Cell-based assay	65%	Thymoma, small-cell lung carcinoma
$GABA_B$ receptor[13]	Limbic encephalitis	Cell-based assay	50%	Small-cell lung carcinoma
$GABA_A$ receptor[14]	Encephalitis	Cell-based assay	<5%	Thymoma
mGluR5[15]	Encephalitis	Cell-based assay	70%	Hodgkin's lymphoma
Dopamine 2 receptor[16]	Basal ganglia encephalitis	Cell-based assay	0%	..
Antibodies against ion channels and other cell-surface proteins				
LGI1[17]	Limbic encephalitis	Cell-based assay	5–10%	Thymoma
CASPR2[18]	Morvan's syndrome‖ or limbic encephalitis	Cell-based assay	20–50%	Thymoma**
DPPX[19]	Encephalitis††	Cell-based assay	<10%	Lymphoma
MOG[20]‡‡	Acute disseminated encephalomyelitis	Cell-based assay	0%	..
Aquaporin 4[21]‡‡	Encephalitis	Cell-based assay	0%	..
GQ1b[22]	Bickerstaff's brainstem encephalitis	ELISA	0%	..

Anti-NMDA receptor encephalitis

- Encephalitis associated with **CSF IgG antibodies** against the GLuN1 subunit of the **NMDA receptor**
- Good correlation between Ab levels and symptoms
- Associated with tumor (50%)

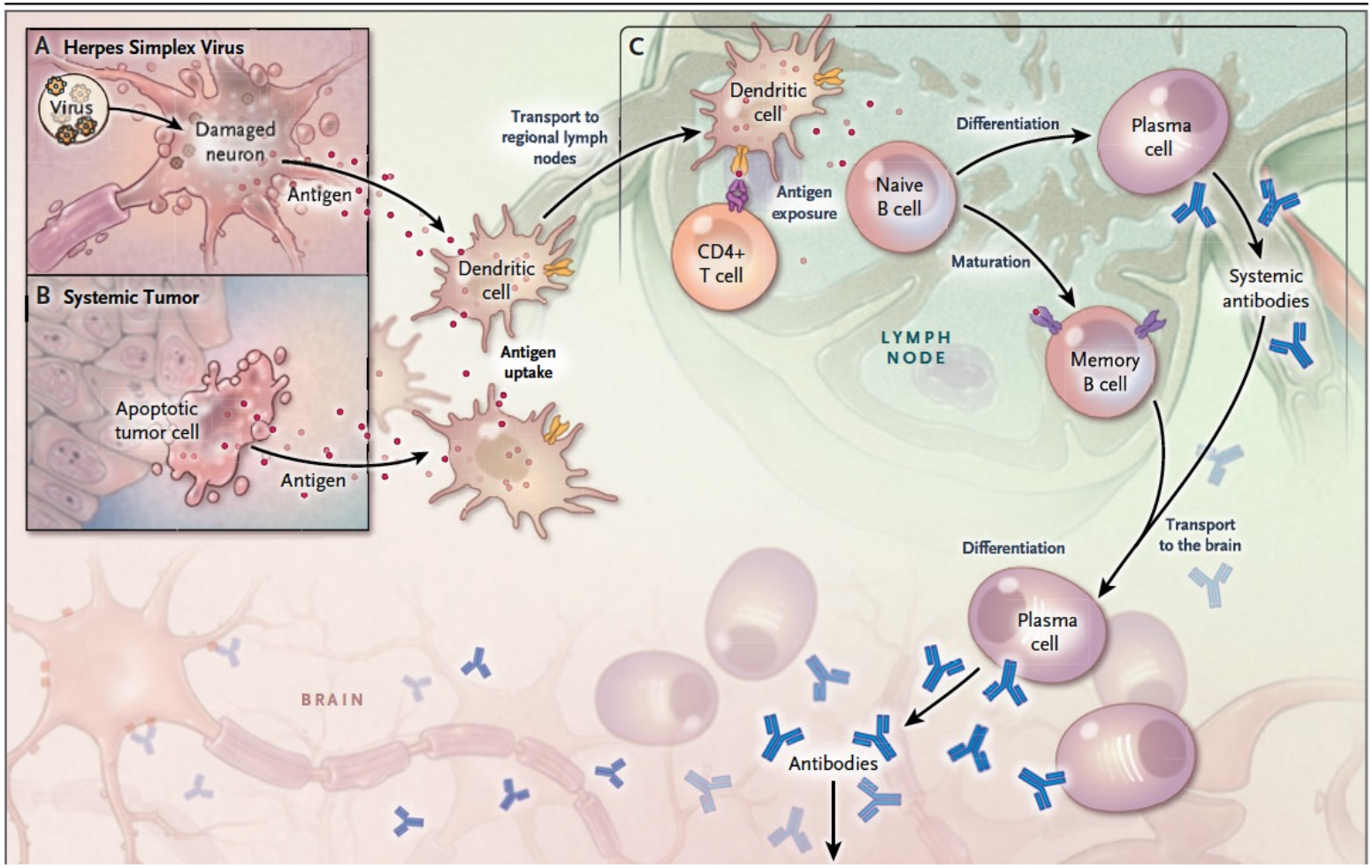




J Dalmau, Lancet Neurol 2011

Antibody-Mediated Encephalitis

Josep Dalmau, M.D., Ph.D., and Francesc Graus, M.D., Ph.D.



NEJM 2018

Anti–*N*-Methyl-D-Aspartate Receptor Encephalitis in Adult Patients Requiring Intensive Care

Etienne de Montmollin[1], Sophie Demeret[2], Noëlle Brulé[3], Marie Conrad[4], Frédéric Dailler[5], Nicolas Lerolle[6], Jean-Christophe Navellou[7], Carole Schwebel[8], Mikaël Alves[9], Martin Cour[10], Nicolas Engrand[11], Jean-Marie Tonnelier[12], Eric Maury[13], Stéphane Ruckly[14], Géraldine Picard[15], Véronique Rogemond[15], Éric Magalhaes[16], Tarek Sharshar[17], Jean-François Timsit[14,16], Jérôme Honnorat[15,18]*, and Romain Sonneville[16,19]*; on behalf of the ENCEPHALITICA Study Group‡

Variable	N= 77 patients
Age, years	24 (20-31)
Female sex	68/76 (89%)
GCS, median (IQR)	11 (7-13)
Seizures / status epilepticus	30 (76%)
CSF WBC, n / mm3	36 (9-112)
CSF protein levels, g/l	0.4 (0.3-0.6)
Normal CT scan	49/62 (95%)
Normal brain MRI	56 / 75 (75%)

Variable	N= 77 patients
Presence of tumor	36/76 (47)
Delay between ICU admission and tumor resection, median (IQR) days	24 (14-51)

Am j Resp Crit Care Med 2017

Anti–*N*-Methyl-D-Aspartate Receptor Encephalitis in Adult Patients Requiring Intensive Care

Etienne de Montmollin[1], Sophie Demeret[2], Noëlle Brulé[3], Marie Conrad[4], Frédéric Dailler[5], Nicolas Lerolle[6], Jean-Christophe Navellou[7], Carole Schwebel[8], Mikaël Alves[9], Martin Cour[10], Nicolas Engrand[11], Jean-Marie Tonnelier[12], Eric Maury[13], Stéphane Ruckly[14], Géraldine Picard[15], Véronique Rogemond[15], Éric Magalhaes[16], Tarek Sharshar[17], Jean-François Timsit[14,16], Jérôme Honnorat[15,18*], and Romain Sonneville[16,19*]; on behalf of the ENCEPHALITICA Study Group[‡]

Variable	N= 77 patients
Delay between ICU admission and immunotherapy, median (IQR) days	8 (2-16)
First-line immunotherapy	
Steroids	61/74 (82%)
IVIg	71/74 (89%)
Plasma exchange	17/74 (23%)
Second-line immunotherapy	
Cyclophosphamide	6/45 (13%)
Rituximab	24/45 (53%)
Both	15/45 (33%)

Am j Resp Crit Care Med 2017

Anti–*N*-Methyl-D-Aspartate Receptor Encephalitis in Adult Patients Requiring Intensive Care

Etienne de Montmollin[1], Sophie Demeret[2], Noëlle Brulé[3], Marie Conrad[4], Frédéric Dailler[5], Nicolas Lerolle[6], Jean-Christophe Navellou[7], Carole Schwebel[8], Mikaël Alves[9], Martin Cour[10], Nicolas Engrand[11], Jean-Marie Tonnelier[12], Eric Maury[13], Stéphane Ruckly[14], Géraldine Picard[15], Véronique Rogemond[15], Éric Magalhaes[16], Tarek Sharshar[17], Jean-François Timsit[14,16], Jérôme Honnorat[15,18]*, and Romain Sonneville[16,19]*; on behalf of the ENCEPHALITICA Study Group[‡]

Multivariate analysis of factors of good neurological outcome at 6 months (mRS < 2)

Variable	Odds Ratio (95% CI)	*P* Value
First-line immunotherapy		0.008
Late immunotherapy	Reference	
Early* intravenous immunoglobulin administration only	3.33 (0.66–16.79)	0.14†
Early* steroid administration only	4.96 (0.76–32.23)	0.09†
Early* combined immunotherapy‡ administration	16.16 (3.32–78.64)	<0.001†
Second-line immunotherapy	0.19 (0.05–0.69)	0.01
White blood cells in first CSF		0.04
>50 cells/mm^3	Reference	
5–50 cells/mm^3	3.97 (1.16–13.65)	0.03†
<5 cells/mm^3	9.83 (1.07–90.65)	0.04†

*before ICU admission or following 8 days of ICU admission

Am j Resp Crit Care Med 2017

JAMA Neurology | Original Investigation

Use and Safety of Immunotherapeutic Management of *N*-Methyl-D-Aspartate Receptor Antibody Encephalitis
A Meta-analysis

Margherita Nosadini, MD, PhD; Michael Eyre, MD; Erika Molteni, PhD; Terrence Thomas, MD; Sarosh R. Irani, MD, PhD; Josep Dalmau, MD, PhD; Russell C. Dale, MD, PhD; Ming Lim, MD, PhD; and the International NMDAR Antibody Encephalitis Consensus Group

N=1552 patients from 652 articles

1105/1508 female patients (73%)

707/1526 aged < 18 years (46%)

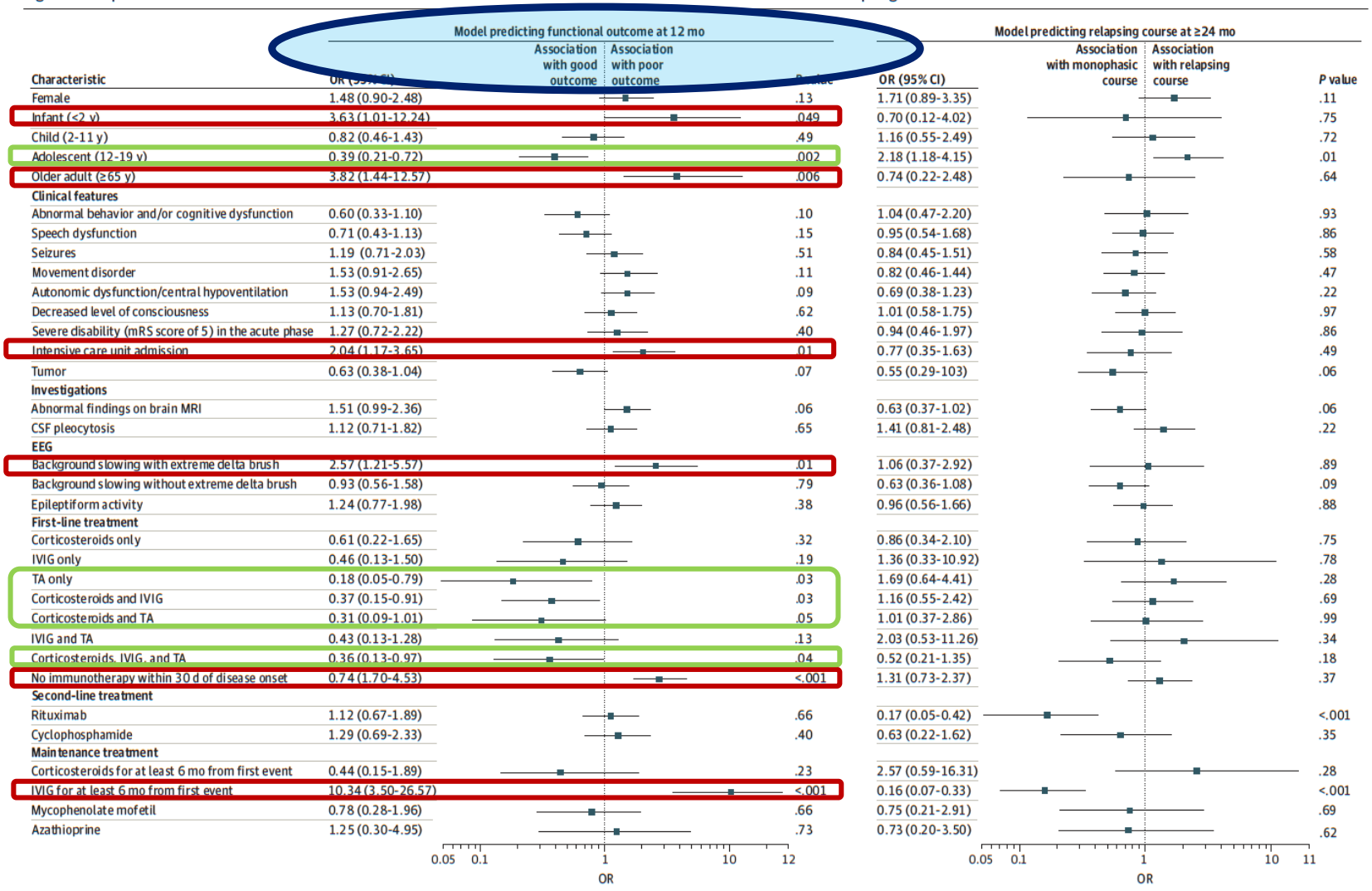
Median age at onset: 20 (0-85) years

389/1524 patients (25.6%) had a tumor (ovarian tumor 324/1524 (21%))

ICU admission : 488/964 (50.6%)

JAMA Neurol. doi:10.1001/jamaneurol.2021.3188
Published online September 20, 2021.

Figure 2. Independent Association of Clinical Characteristics and Treatment Factors With Functional Outcome at 12 Months and Relapsing Disease Course at 24 Months and Later

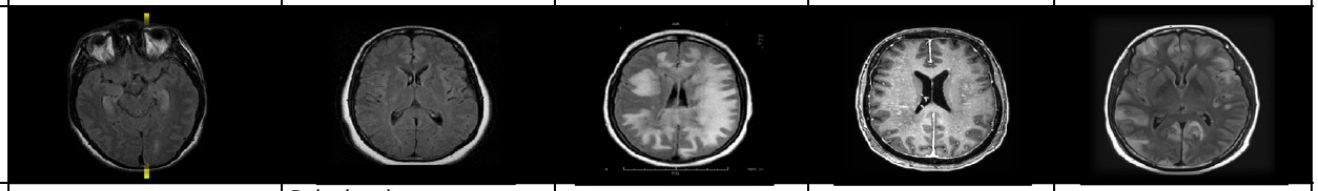


Characteristic	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Female	1.48 (0.90-2.48)	.13	1.71 (0.89-3.35)	.11
Infant (<2 y)	3.63 (1.01-12.24)	.049	0.70 (0.12-4.02)	.75
Child (2-11 y)	0.82 (0.46-1.43)	.49	1.16 (0.55-2.49)	.72
Adolescent (12-19 y)	0.39 (0.21-0.72)	.002	2.18 (1.18-4.15)	.01
Older adult (≥65 y)	3.82 (1.44-12.57)	.006	0.74 (0.22-2.48)	.64
Clinical features				
Abnormal behavior and/or cognitive dysfunction	0.60 (0.33-1.10)	.10	1.04 (0.47-2.20)	.93
Speech dysfunction	0.71 (0.43-1.13)	.15	0.95 (0.54-1.68)	.86
Seizures	1.19 (0.71-2.03)	.51	0.84 (0.45-1.51)	.58
Movement disorder	1.53 (0.91-2.65)	.11	0.82 (0.46-1.44)	.47
Autonomic dysfunction/central hypoventilation	1.53 (0.94-2.49)	.09	0.69 (0.38-1.23)	.22
Decreased level of consciousness	1.13 (0.70-1.81)	.62	1.01 (0.58-1.75)	.97
Severe disability (mRS score of 5) in the acute phase	1.27 (0.72-2.22)	.40	0.94 (0.46-1.97)	.86
Intensive care unit admission	2.04 (1.17-3.65)	.01	0.77 (0.35-1.63)	.49
Tumor	0.63 (0.38-1.04)	.07	0.55 (0.29-103)	.06
Investigations				
Abnormal findings on brain MRI	1.51 (0.99-2.36)	.06	0.63 (0.37-1.02)	.06
CSF pleocytosis	1.12 (0.71-1.82)	.65	1.41 (0.81-2.48)	.22
EEG				
Background slowing with extreme delta brush	2.57 (1.21-5.57)	.01	1.06 (0.37-2.92)	.89
Background slowing without extreme delta brush	0.93 (0.56-1.58)	.79	0.63 (0.36-1.08)	.09
Epileptiform activity	1.24 (0.77-1.98)	.38	0.96 (0.56-1.66)	.88
First-line treatment				
Corticosteroids only	0.61 (0.22-1.65)	.32	0.86 (0.34-2.10)	.75
IVIG only	0.46 (0.13-1.50)	.19	1.36 (0.33-10.92)	.78
TA only	0.18 (0.05-0.79)	.03	1.69 (0.64-4.41)	.28
Corticosteroids and IVIG	0.37 (0.15-0.91)	.03	1.16 (0.55-2.42)	.69
Corticosteroids and TA	0.31 (0.09-1.01)	.05	1.01 (0.37-2.86)	.99
IVIG and TA	0.43 (0.13-1.28)	.13	2.03 (0.53-11.26)	.34
Corticosteroids, IVIG, and TA	0.36 (0.13-0.97)	.04	0.52 (0.21-1.35)	.18
No immunotherapy within 30 d of disease onset	0.74 (1.70-4.53)	<.001	1.31 (0.73-2.37)	.37
Second-line treatment				
Rituximab	1.12 (0.67-1.89)	.66	0.17 (0.05-0.42)	<.001
Cyclophosphamide	1.29 (0.69-2.33)	.40	0.63 (0.22-1.62)	.35
Maintenance treatment				
Corticosteroids for at least 6 mo from first event	0.44 (0.15-1.89)	.23	2.57 (0.59-16.31)	.28
IVIG for at least 6 mo from first event	10.34 (3.50-26.57)	<.001	0.16 (0.07-0.33)	<.001
Mycophenolate mofetil	0.78 (0.28-1.96)	.66	0.75 (0.21-2.91)	.69
Azathioprine	1.25 (0.30-4.95)	.73	0.73 (0.20-3.50)	.62

Results from the bootstrapped logistic regression models are displayed. Adjusted odds ratios (ORs), 95% CIs, and *P* values were derived from the distributions of the regression coefficients over 10 000 folds. CSF indicates cerebrospinal fluid; EEG, electroencephalography; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; TA, therapeutic apheresis.

Understanding auto-immune encephalitis in the ICU

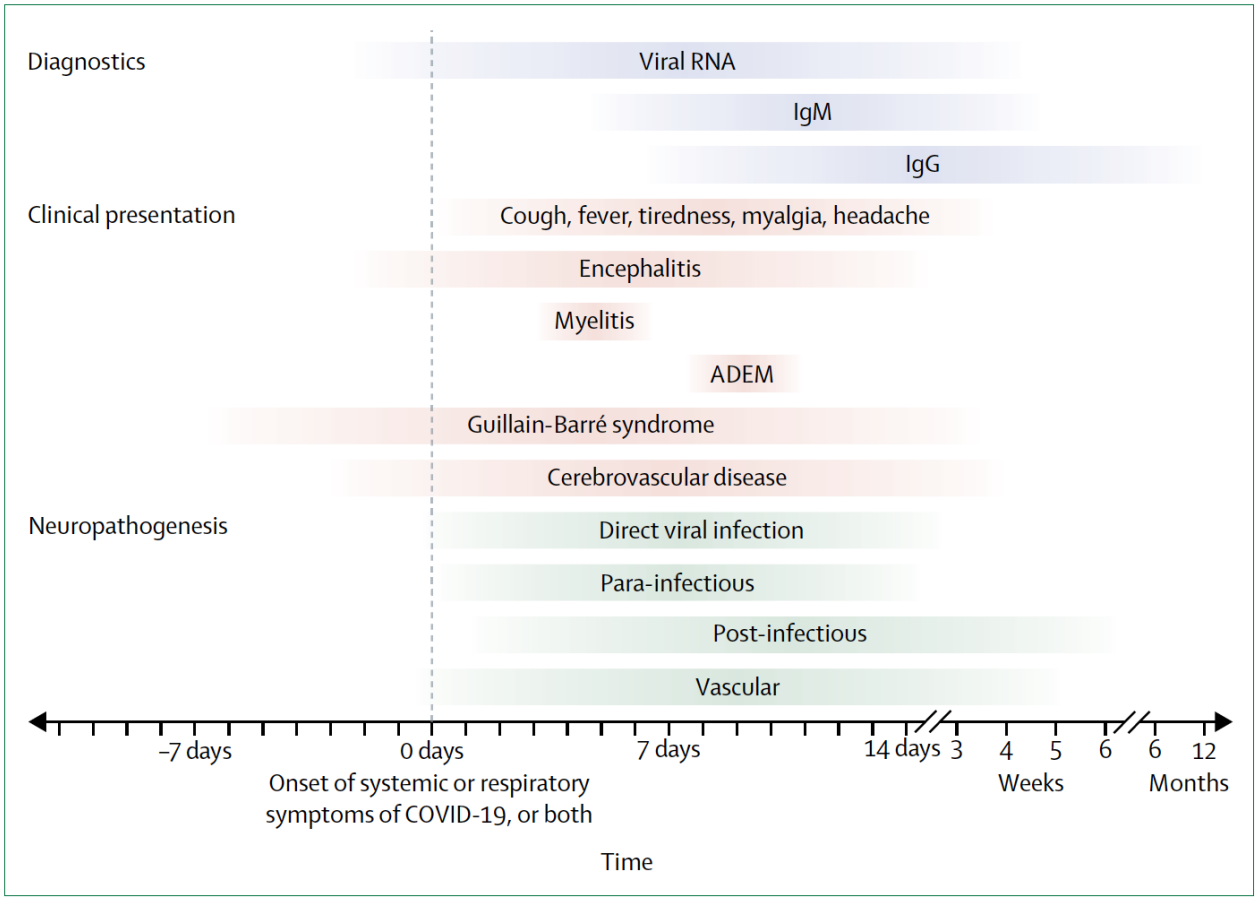
R. Sonneville[1,2*], A. Venkatesan[3] and J. Honnorat[4,5]

	Limbic	Anti-NMDAR	ADEM	Anti-GFAP	Anti-$GABA_AR$
Epidemiology	Adults	Children/young adults Female to male ratio 4/1	Children/young adults	Children/young adults	Children/young adults Female to male ratio 1/5
History	Subacute onset	Prodromal viral illness Subacute or acute onset	Acute onset	Acute onset	Subacute or acute onset
Trigger	Tumor (50 - 95%)	Tumor (50%) HSV encephalitis	Systemic infection Vaccination	Unknown	Unknown
Signs	Memory deficit Seizures Psychiatric symptoms	Behavioral changes Psychosis Movement disorders Seizures Autonomic dysfunction	Encephalopathy Fever Focal signs Myelopathy Optic neuritis	Encephalopathy Fever Focal signs Myelopathy Optic neuritis	Seizures Refractory status epilepticus
MRI					
EEG	Temporal ictal or slow-wave activity	Delta brush Generalized rhythmic delta activity Excessive beta activity	Diffuse or focal slow-wave activity	Diffuse or focal slow-wave activity	Ictal activity Diffuse or focal slow-wave activity
Abs	Anti- LGI1, $GABA_B$-R or AMPA-R CSF and/or serum	Anti-NMDAR in CSF	Anti-MOG in serum (50%)	Anti-GFAP in CSF	Anti-$GABA_AR$ in CSF and/or serum
Rx	1st: steroids + IgIV or PLEX 2nd: rituximab or cyclophosphamide	1st: steroids + IgIV or PLEX 2nd: rituximab or cyclophosphamide	1st line: steroids 2nd line: PLEX	1st line: steroids 2nd line: PLEX	1st line: steroids 2nd line: PLEX

Intensive Care Medicine 2019

Neurological associations of COVID-19

Mark A Ellul, Laura Benjamin, Bhagteshwar Singh, Suzannah Lant, Benedict Daniel Michael, Ava Easton, Rachel Kneen, Sylviane Defres, Jim Sejvar, Tom Solomon

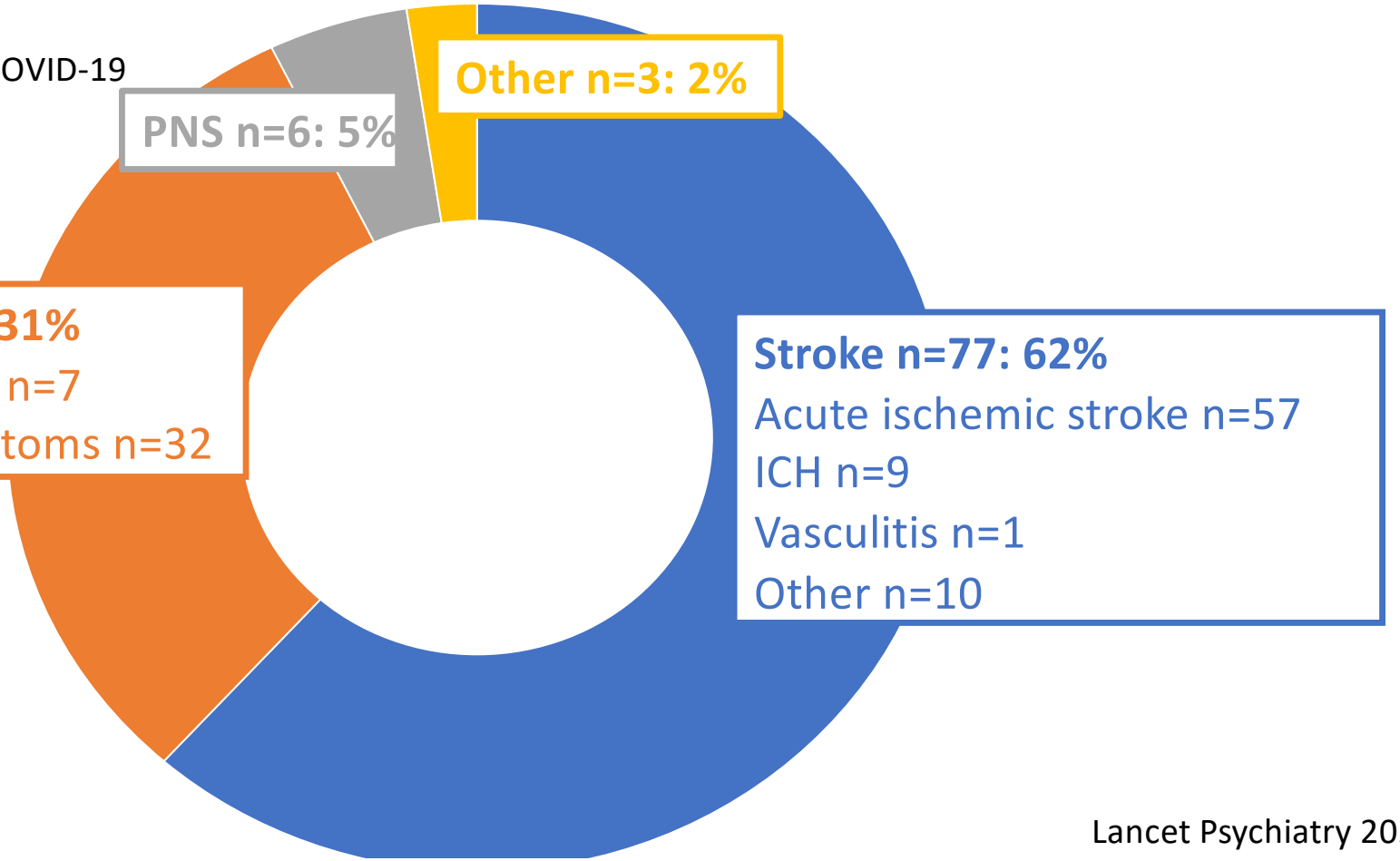


Lancet Neurol 2020

Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study

Aravinthan Varatharaj, Naomi Thomas, Mark A Ellul, Nicholas W S Davies, Thomas A Pollak, Elizabeth L Tenorio, Mustafa Sultan, Ava Easton, Gerome Breen, Michael Zandi, Jonathan P Coles, Hadi Manji, Rustam Al-Shahi Salman, David K Menon, Timothy R Nicholson, Laura A Benjamin, Alan Carson, Craig Smith, Martin R Turner, Tom Solomon, Rachel Kneen, Sarah L Pett, Ian Galea, Rhys H Thomas*, Benedict D Michael*, on behalf of the CoroNerve Study Group†*

Nationwide surveillance study of acute neurological
and psychiatric complications of COVID-19
N=135 patients



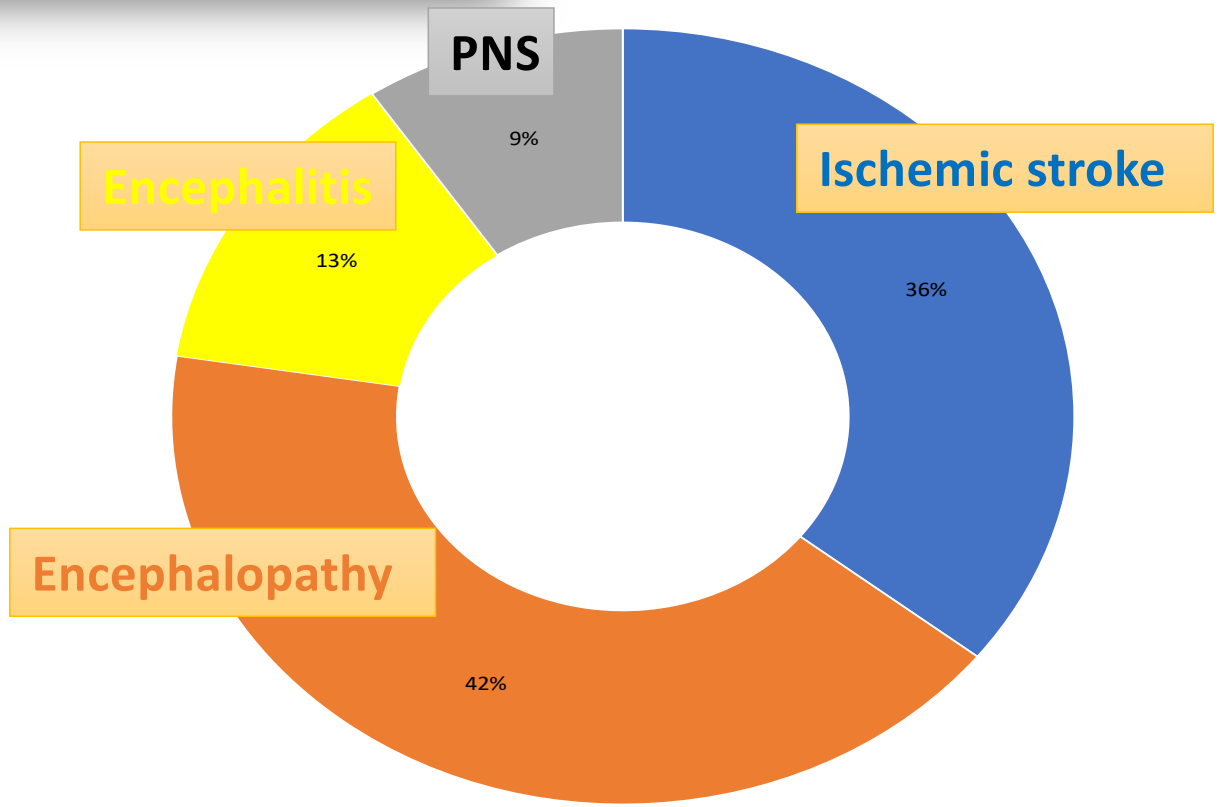
Lancet Psychiatry 2020

Original article

Neurologic manifestations associated with COVID-19: a multicentre registry

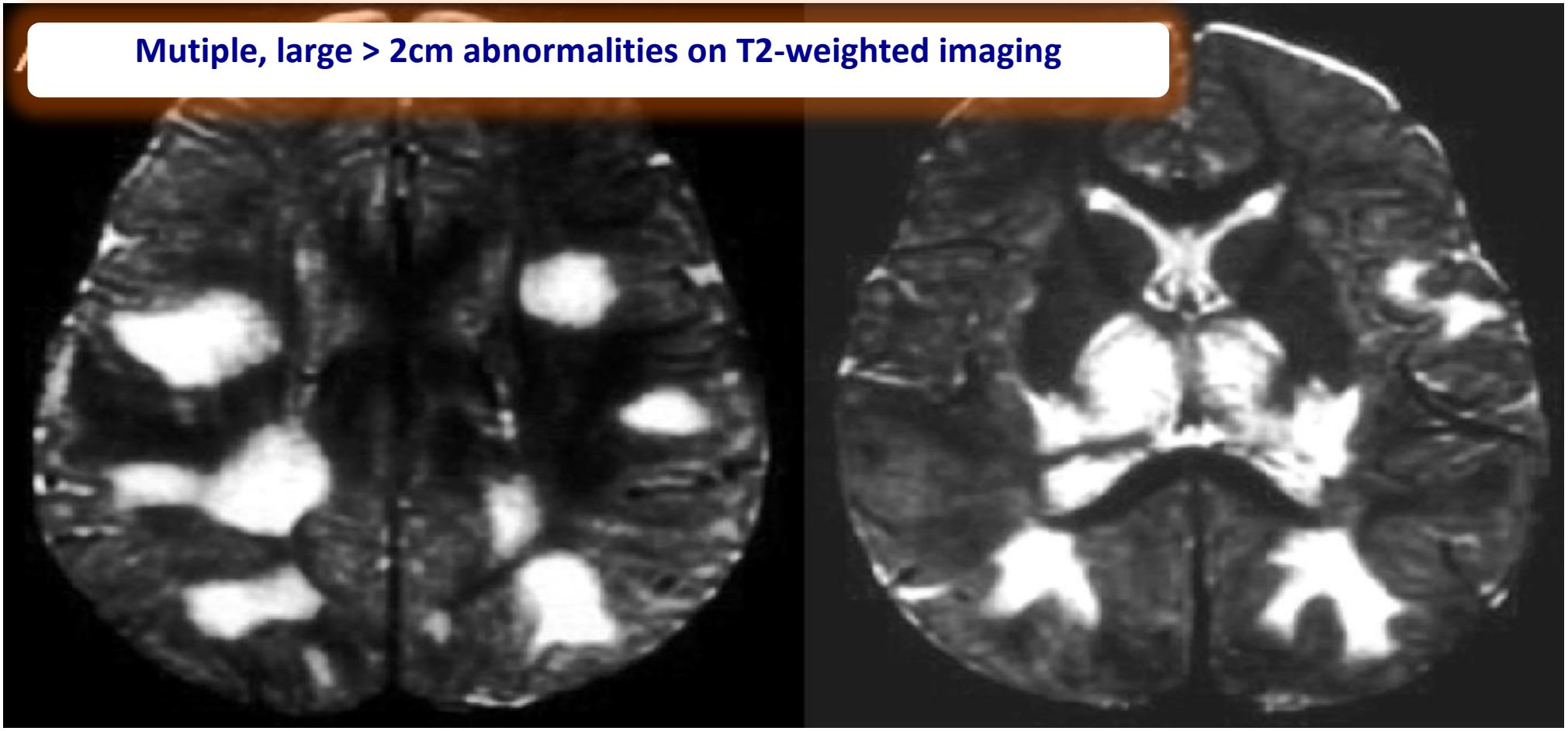
Elodie Meppiel [1,*], Nathan Peiffer-Smadja [2,3], Alexandra Maury [1], Imen Bekri [4], Cécile Delorme [5], Virginie Desestret [6], Lucas Gorza [7], Geoffroy Hautecloque-Raysz [8], Sophie Landre [9], Annie Lannuzel [10], Solène Moulin [11], Peggy Perrin [12], Paul Petitgas [13], François Sellal [8], Adrien Wang [7], Pierre Tattevin [13], Thomas de Broucker [1], on behalf of the contributors to the NeuroCOVID registry*

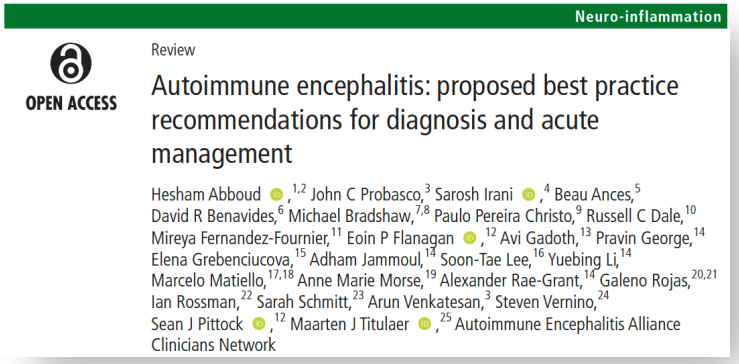
N=222 patients



Clinical Microbiology and Infection 2020

Mutiple, large > 2cm abnormalities on T2-weighted imaging





Neuro-inflammation

OPEN ACCESS

Review

Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management

Hesham Abboud ,[1,2] John C Probasco,[3] Sarosh Irani ,[4] Beau Ances,[5] David R Benavides,[6] Michael Bradshaw,[7,8] Paulo Pereira Christo,[9] Russell C Dale,[10] Mireya Fernandez-Fournier,[11] Eoin P Flanagan ,[12] Avi Gadoth,[13] Pravin George,[14] Elena Grebenciucova,[15] Adham Jammoul,[14] Soon-Tae Lee,[16] Yuebing Li,[14] Marcelo Matiello,[17,18] Anne Marie Morse,[19] Alexander Rae-Grant,[14] Galeno Rojas,[20,21] Ian Rossman,[22] Sarah Schmitt,[23] Arun Venkatesan,[3] Steven Vernino,[24] Sean J Pittock ,[12] Maarten J Titulaer ,[25] Autoimmune Encephalitis Alliance Clinicians Network

Box 1 Best practice recommendations summary for acute management of autoimmune encephalitis (AE)

Severe presentation* = combination therapy

*severe NMDARE, refractory status epilepticus, severe dysautonomia …

FIRST LINE
High dose corticosteroids
+
IgIV or PLEX

No improvement ?

SECOND LINE
Rituximab
OR
Cyclophosphamide

IVIG first if agitation or bleeding disorders
PLEX first if hyponatremia, high risk of thrombosis,
or brain/spinal demyelination

Rituximab in known or highly suspected antibody-mediated immunity (e.g. NMDARE)
Cyclophosphamide in case of cell-mediated immunity (classical paraneoplastic syndromes)

J Neurol Neurosurg Psychiatry 2021

Encéphalites aiguës

De quoi parle-t-on ?

Epidémiologie et pronostic

Prise en charge initiale

Causes principales justifiant un traitement spécifique

Mesures symptomatiques

Pronostic à long terme

Conclusion

Early-onset status epilepticus in patients with acute encephalitis

Romain Sonneville, MD, PhD*, Eric Mariotte, MD, Mathilde Neuville, MD, Sébastien Minaud, MD, Eric Magalhaes, MD, Stéphane Ruckly, BSc, Marie Cantier, MD, Guillaume Voiriot, MD, PhD, Aguila Radjou, MD, Roland Smonig, MD, Jean-François Soubirou, MD, Bruno Mourvillier, MD, Lila Bouadma, MD, PhD, Michel Wolff, MD, Jean-François Timsit, MD, PhD

N=290 patients with encephalitis, Bichat medical ICU, Paris, France

Convulsive status epilepticus = 20%

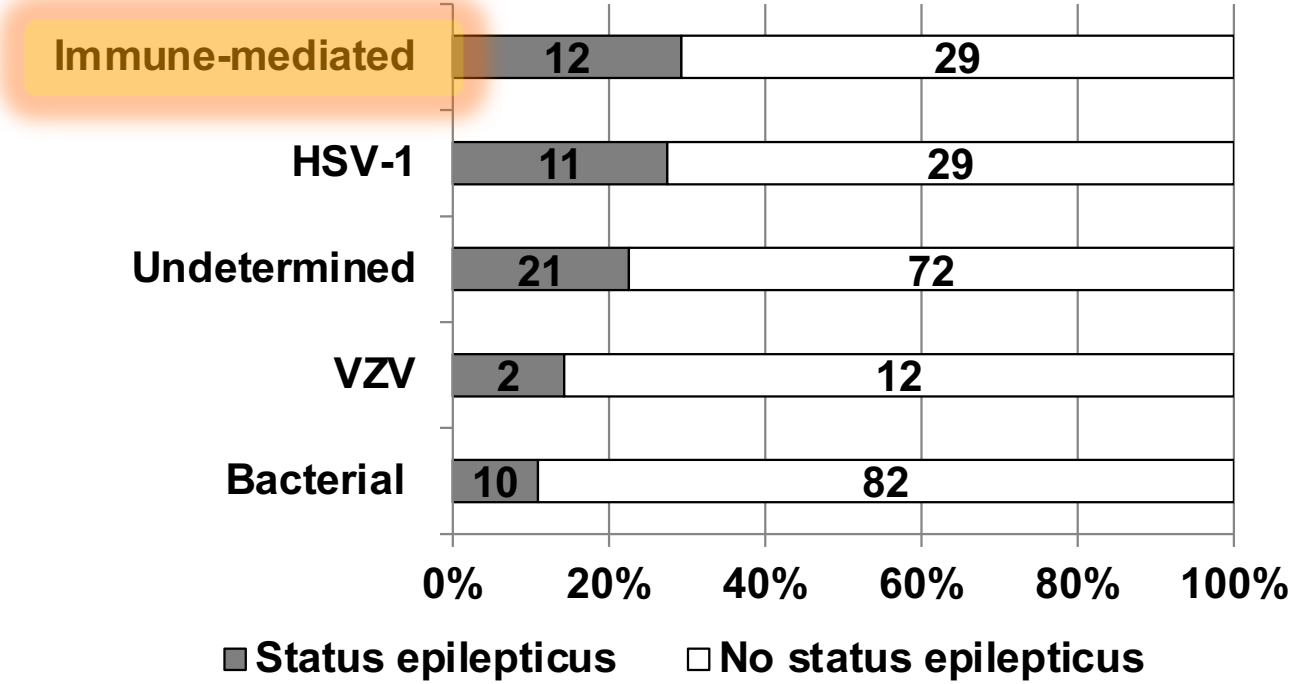


Figure 1. Cause-specific prevalence of status epilepticus in adults with encephalitis. HSV = Herpes simplex virus, VZV = Varicella-zoster virus.

Medicine 2016

Intensive Care Med
DOI 10.1007/s00134-013-2938-4

SYSTEMATIC REVIEW

Jan Claassen
Fabio S. Taccone
Peter Horn
Martin Holtkamp
Nino Stocchetti
Mauro Oddo

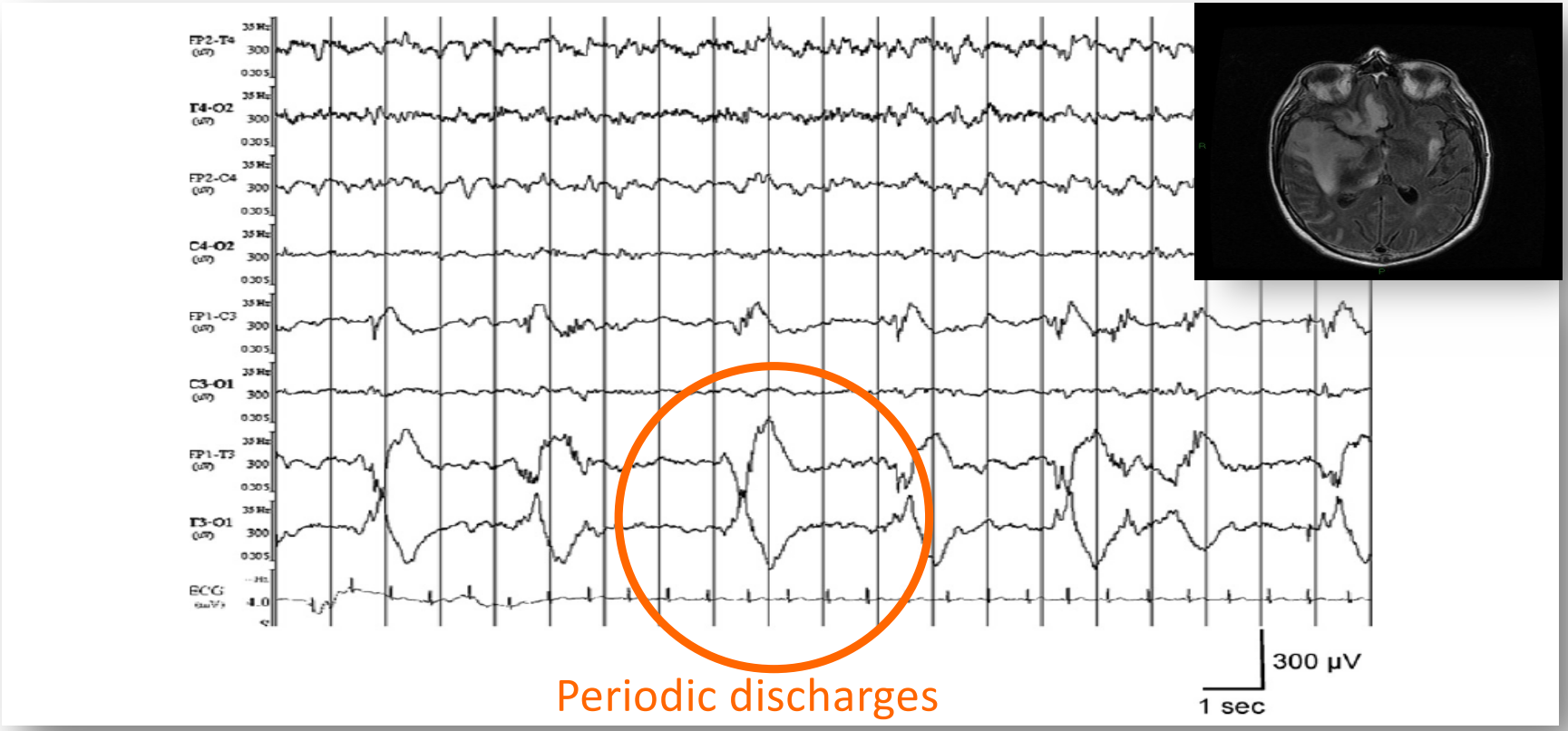
Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM

Recommendations for patients with infectious and non-infectious encephalitis

1. We recommend EEG in patients with encephalitis that are comatose or have unexplained neurological deficits to rule out NCSz (strong recommendation, low quality of evidence—grade 1C).
2. We suggest EEG in patients with encephalitis to assist with prognosis (weak recommendation, very low quality of evidence—grade 2D).

2013

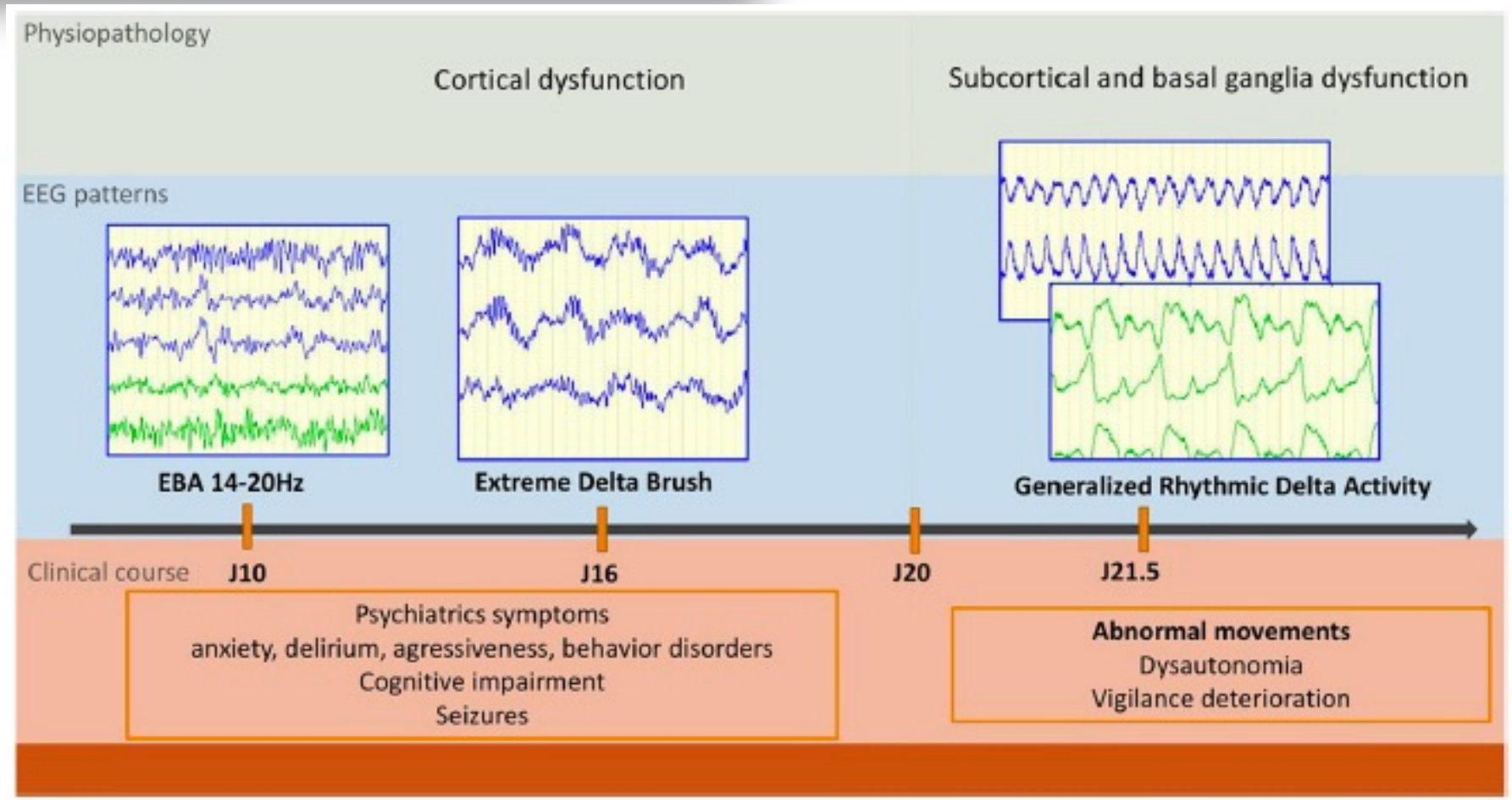
Electroencephalography for diagnosis and prognosis of acute encephalitis ☆



R Sutter, Clin neurophysiology 2014

EEG analysis in anti-NMDA receptor encephalitis: Description of typical patterns

S. Jeannin-Mayer [a,*], N. André-Obadia [b,g], S. Rosenberg [c], C. Boutet [d], J. Honnorat [e,f], J.C. Antoine [a], L. Mazzola [a,g]



S. Jeannin-Mayer et al./Clinical Neurophysiology 130 (2019) 289–296

Encéphalites aiguës

De quoi parle-t-on ?

Epidémiologie et pronostic

Prise en charge initiale

Causes principales justifiant un traitement spécifique

Mesures symptomatiques

Pronostic à long terme

Conclusion

ORIGINAL

Functional outcomes in adult patients with herpes simplex encephalitis admitted to the ICU: a multicenter cohort study

P. Jaquet[1], E. de Montmollin[1,2], C. Dupuis[1,2], C. Sazio[3], M. Conrad[4], V. Susset[5], S. Demeret[6], J. M. Tadie[7], L. Argaud[8], F. Barbier[9], B. Sarton[10], R. Chabane[11], D. Daubin[12], N. Brulé[13], N. Lerolle[14], M. Alves[15], D. Da Silva[16], A. El Kalioubi[17], S. Silva[10], P. Bailly[18], M. Wolff[1], L. Bouadma[1,2], J. F. Timsit[1,2], R. Sonneville[1,19*] and ENCEPHALITICA study group

Marechal J, Mourvillier B, Dailler F, Bruneel F, Lautrette A, Novy E, Guidet B, Mateos F, Brault C, Maestraggi Q, Razazi K, Quenot JP, Joret A, Levrat A, Massri A, Robert A, Contou D, Mira JP, Stephane G, Voiriot G, Berger A, Das V, Engrand N, Murgier M, Siami S, Hraiech S, Mariotte E, Ragot C, Stoclin A, Trouiller P, Schmidt M.

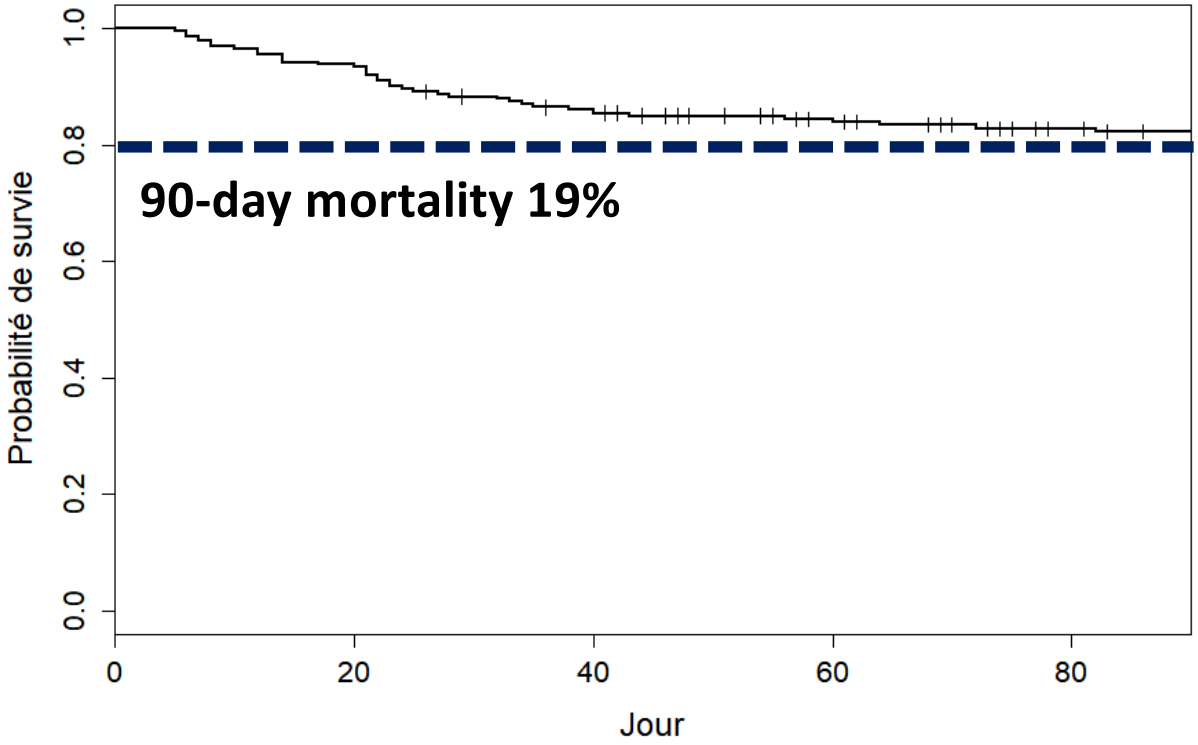
P Jaquet et al. Intensive care medicine 2019

Functional outcomes in adult patients with herpes simplex encephalitis admitted to the ICU: the HERPETICS multicenter study

N= 259 patients with HSV encephalitis admitted to the **ICU**
Multicenter study, 46 ICUs, France, 2006-2016

90-day mRankin scale score

mRS 0-2	mRS 3-6
74 (29%) pts	185 (71) % pts



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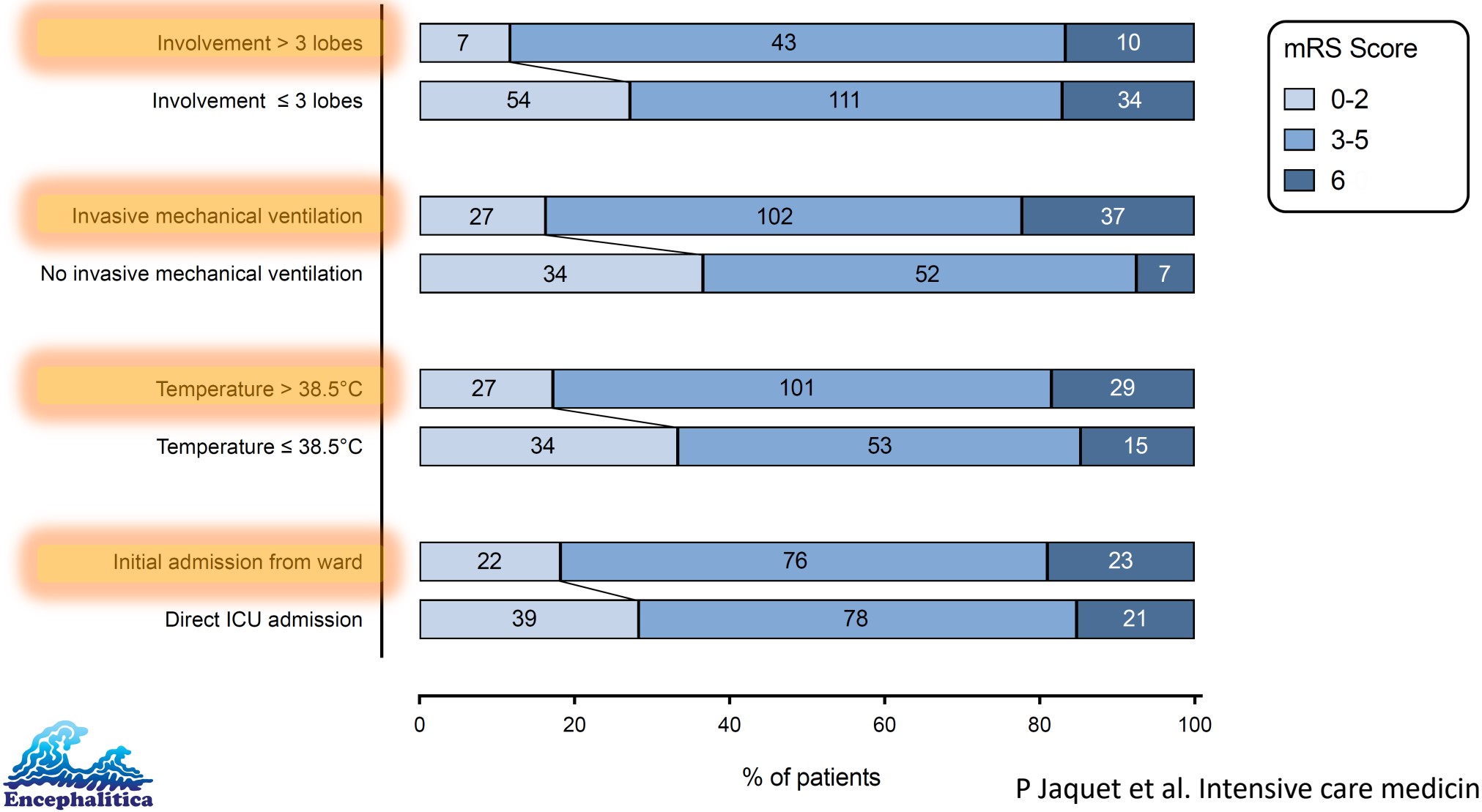

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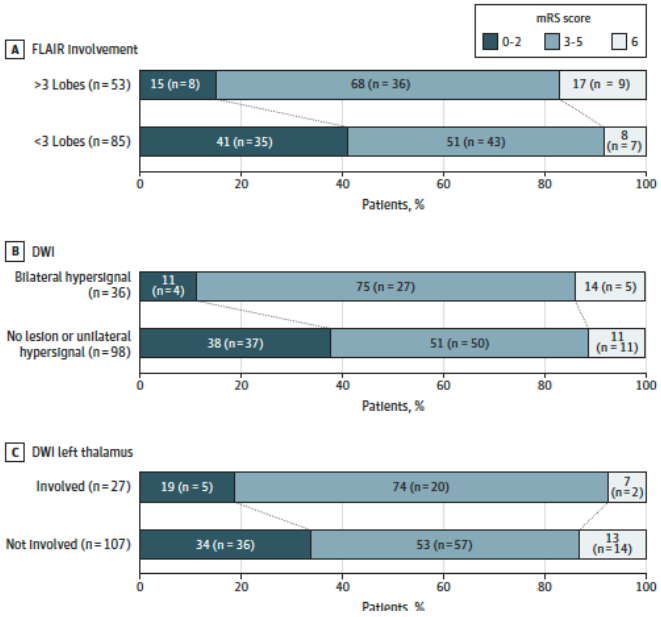
JAMA Network Open

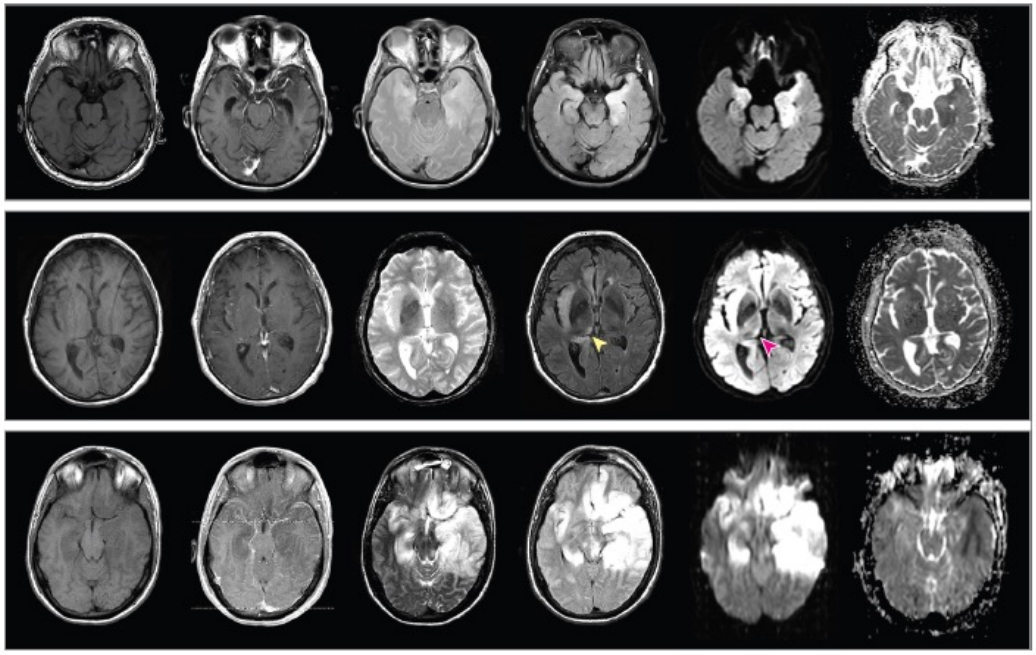
Original Investigation | Critical Care Medicine

Assessment of Magnetic Resonance Imaging Changes and Functional Outcomes Among Adults With Severe Herpes Simplex Encephalitis

Benjamine Sarton, MD; Pierre Jaquet, MD; Djida Belkacemi, MD; Etienne de Montmollin, MD, PhD; Fabrice Bonneville, MD, PhD; Charline Sazio, MD; Aurelien Frérou, MD; Marie Conrad, MD; Delphine Daubin, MD; Russell Chabanne, MD; Laurent Argaud, MD, PhD; Frédéric Dailler, MD; Noëlle Brulé, MD; Nicolas Lerolle, MD; Quentin Maestraggi, MD; Julien Marechal, MD; Pierre Bailly, MD; Keyvan Razazi, MD; Francois Mateos, MD; Bertrand Guidet, MD, PhD; Albrice Levrat, MD; Vincent Susset, MD; Alexandre Lautrette, MD, PhD; Jean-Paul Mira, MD, PhD; Ahmed El Kalioubie, MD; Alexandre Robert, MD, PhD; Alexandre Massri, MD; Jean François Albucher, MD; Jean Marc Olivot, MD, PhD; Jean Marie Conil, MD, PhD; Lila Boudma, MD, PhD; Jean-François Timsit, MD, PhD; Romain Sonneville, MD, PhD; Stein Silva, MD, PhD; for the ENCEPHALITICA Consortium

Figure 2. Distribution of Modified Rankin Scale (mRS) at Day 90 According to Magnetic Resonance Imaging Data

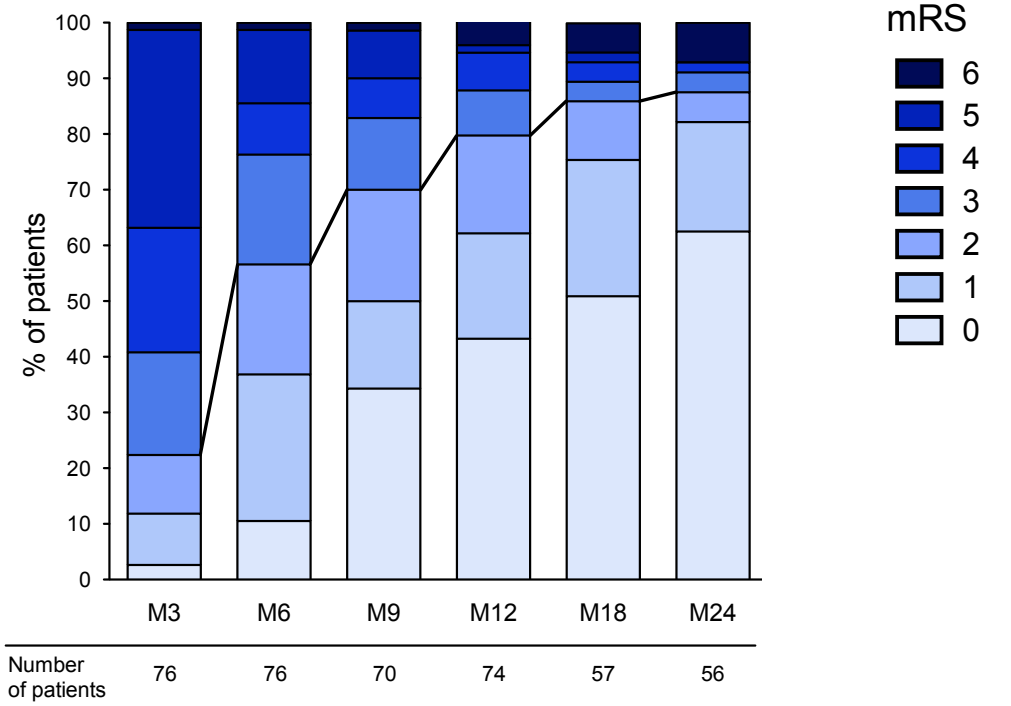




2021

Anti–*N*-Methyl-D-Aspartate Receptor Encephalitis in Adult Patients Requiring Intensive Care

Etienne de Montmollin[1], Sophie Demeret[2], Noëlle Brulé[3], Marie Conrad[4], Frédéric Dailler[5], Nicolas Lerolle[6], Jean-Christophe Navellou[7], Carole Schwebel[8], Mikaël Alves[9], Martin Cour[10], Nicolas Engrand[11], Jean-Marie Tonnelier[12], Eric Maury[13], Stéphane Ruckly[14], Géraldine Picard[15], Véronique Rogemond[15], Éric Magalhaes[16], Tarek Sharshar[17], Jean-François Timsit[14,16], Jérôme Honnorat[15,18]*, and Romain Sonneville[16,19]*; on behalf of the ENCEPHALITICA Study Group‡



Encephalitica

Am j Resp Crit Care Med 2017

ARTICLE OPEN ACCESS

A score that predicts 1-year functional status in patients with anti-NMDA receptor encephalitis

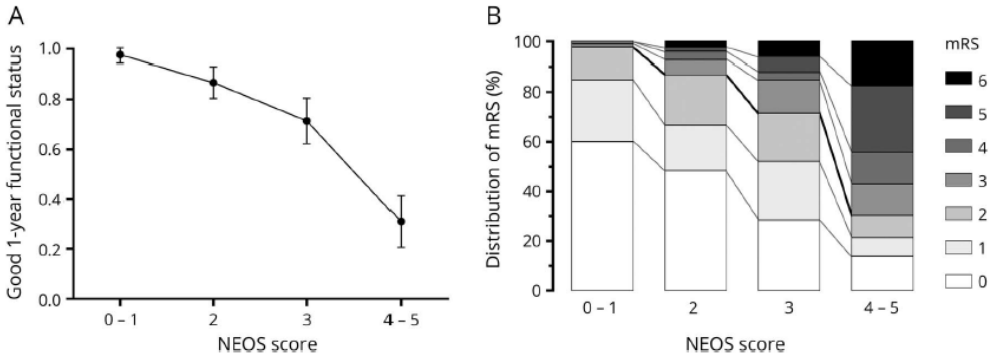
Ramani Balu, MD, PhD, Lindsey McCracken, MS, Eric Lancaster, MD, PhD, Francesc Graus, MD, PhD, Josep Dalmau, MD, PhD,* and Maarten J. Titulaer, MD, PhD*

Correspondence
Prof. Dalmau

Patient characteristic	Odds ratio (95% CI)	*p*	NEOS score points
ICU admission required	5.89 (2.17–15.99)	0.001	1
No clinical improvement after 4 wk of treatment	12.10 (6.38–22.93)	<0.001	1
No treatment within 4 wk of symptom onset	2.52 (1.39–4.55)	0.002	1
Abnormal MRI	2.20 (1.21–3.98)	0.009	1
CSF WBC count >20 cells/μL	2.10 (1.13–3.91)	0.019	1

Abbreviations: CI = confidence interval; ICU = intensive care unit; NEOS = anti-NMDAR Encephalitis One-Year Functional Status; WBC = white blood cell.

Figure 1 NEOS score predicts 1-year functional status



(A) Graph shows the probability of good functional status at 1 year vs NEOS score for all patients in the analyzed cohort. Increasing NEOS score is strongly associated with lower probability of good functional status at 1 year ($p < 0.001$, Cuzick nonparametric test for trend). Error bars represent 95% confidence intervals for each measurement. (B) Distribution of mRS values across NEOS score values. There is a progressive shift toward higher 1-year mRS values with increasing NEOS score. mRS = modified Rankin Scale; NEOS = anti-NMDAR Encephalitis One-Year Functional Status.

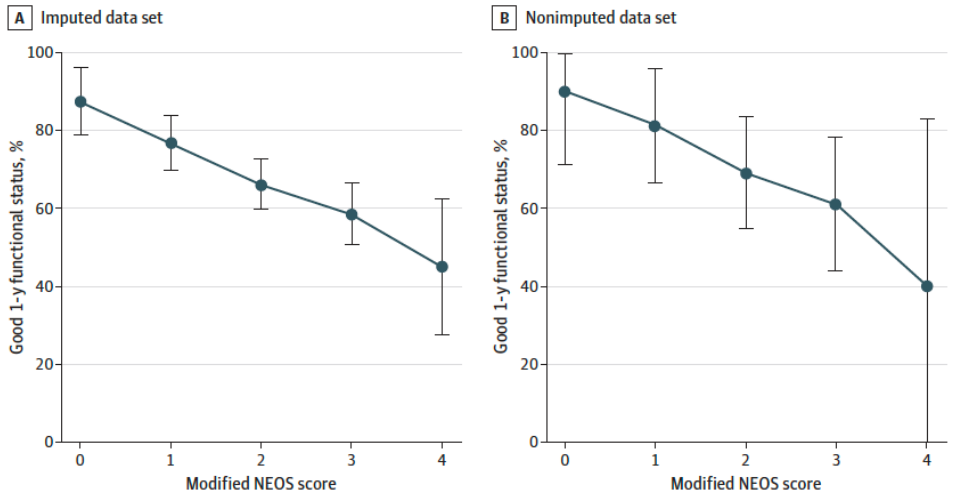
Neurology 2019

JAMA Neurology | Original Investigation

Use and Safety of Immunotherapeutic Management of *N*-Methyl-D-Aspartate Receptor Antibody Encephalitis
A Meta-analysis

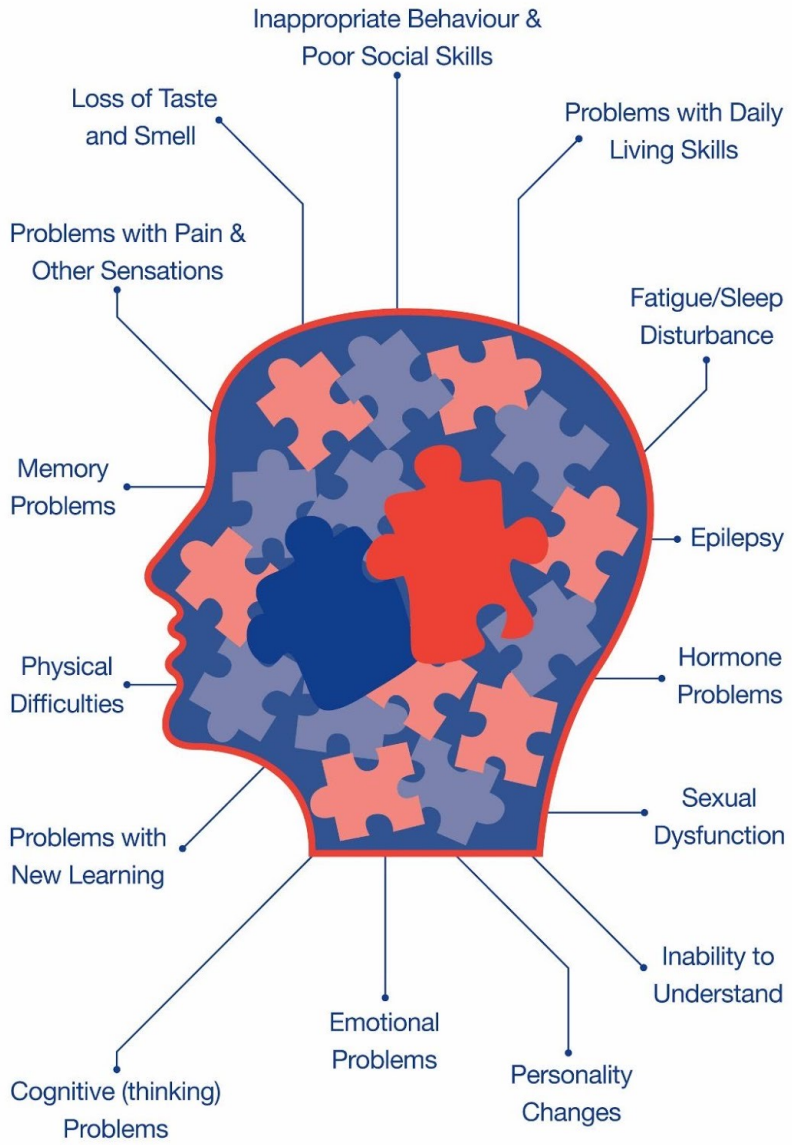
Margherita Nosadini, MD, PhD; Michael Eyre, MD; Erika Molteni, PhD; Terrence Thomas, MD; Sarosh R. Irani, MD, PhD; Josep Dalmau, MD, PhD; Russell C. Dale, MD, PhD; Ming Lim, MD, PhD; and the International NMDAR Antibody Encephalitis Consensus Group

Figure 4. Association Between Modified Anti-NMDAR Encephalitis One-Year Functional Status (NEOS) Score and 1-Year Functional Status



Probability of good functional status (modified Rankin Scale score of 0 to 2) at 1 year after disease onset according to the modified NEOS score for all patients with available data in the imputed (n = 582) and nonimputed (n = 112) data sets. Error bars represent 95% CIs.

JAMA Neurol. doi:10.1001/jamaneurol.2021.3188
Published online September 20, 2021.


Inappropriate Behaviour & Poor Social Skills
Loss of Taste and Smell
Problems with Daily Living Skills
Problems with Pain & Other Sensations
Fatigue/Sleep Disturbance
Memory Problems
Epilepsy
Physical Difficulties
Hormone Problems
Problems with New Learning
Sexual Dysfunction
Inability to Understand
Emotional Problems
Personality Changes
Cognitive (thinking) Problems
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Conclusion …

- **Un syndrome neurologique aigu** associé à une **morbi-mortalité significative**
- **Causes infectieuses** et **dysimmunitaires**
- Prise en charge initiale : **algorithme diagnostique**
- **IRM cérébrale**
- Identifier rapidement les **causes justifiant un traitement spécifique**
- **Mesures symptomatiques**
  - USC / réanimation
  - Mesures de neuroprotection
  - Complications centrales (convulsions) et systémiques

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