Urgences Neurologiques Chez l'Immunodéprimé

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Hôpital Bichat Claude-Bernard AP-HP

iame RESEARCH CENTER ON INFECTIOUS DISEASES

APHP, Hôpital Bichat Claude Bernard, Paris
Intensive Care Medicine

Disclosures

- French Ministry of Health (Grants paid to institution)
- LFB (Research funding)
- ADVANZ PHARMA (Research funding)
- AOP Health (Research funding)
- bioMérieux (Fees)

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- Transplantée cardiaque (CM du post-partum) en avril 2023
- Ttt : corticoides, ciclosporine, mycophénolate
- à 2 mois de la TC : ralentissement psychomoteur sur qq jours
  - Convulsions « inaugurales » + coma post-critique
  - GCS 13
  - Pas de signe focal
  - 37.8° C
  - PA 140/80 mmHg, FC 80/mn

?

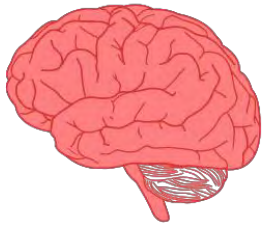
Urgences Neurologiques chez l'Immunodéprimé

1. Une évaluation multimodale rapide
2. Eliminer infection(s) du SNC
3. PRES ?
4. Autre neurotoxicité ?
5. Conclusion

6 points-clés

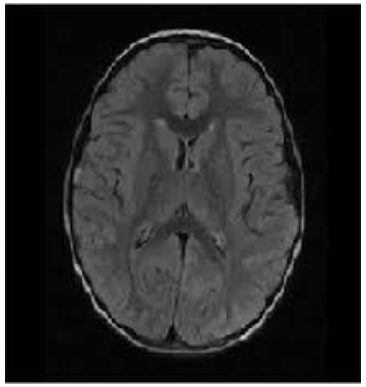
1. **Histoire de l'immunodépression, ATCDs neurologiques ?**
2. **Immunodépression** (λ, CD4….)
3. **Traitement:** Prophylaxie IO ? Observance ?
4. **Mode d'installation** des troubles
5. **Imagerie cérébrale** injectée **(IRM > TDM) d'abord**
6. **LCR : cultures, PCR, NGS …**

→ Approche syndromique

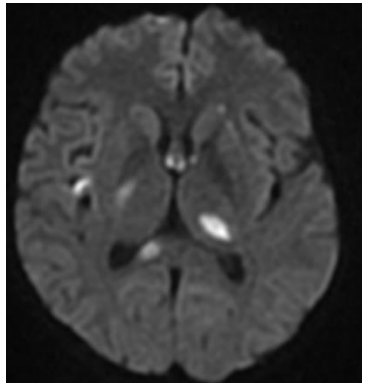


Acute CNS Syndrome ?

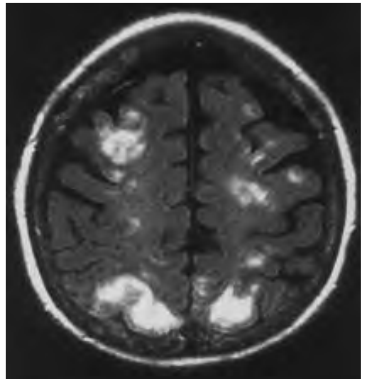
NORMAL MRI



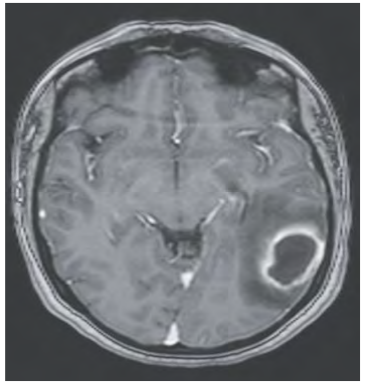
CEREBROVASCULAR LESIONS



WHITE MATTER LESIONS



BRAIN ABSCESS(ES)



Central Nervous System Syndromes in Solid Organ Transplant Recipients

POSTOPERATIVE PHASE
1-2 months
Post operative delirium
Stroke
Drug toxicity

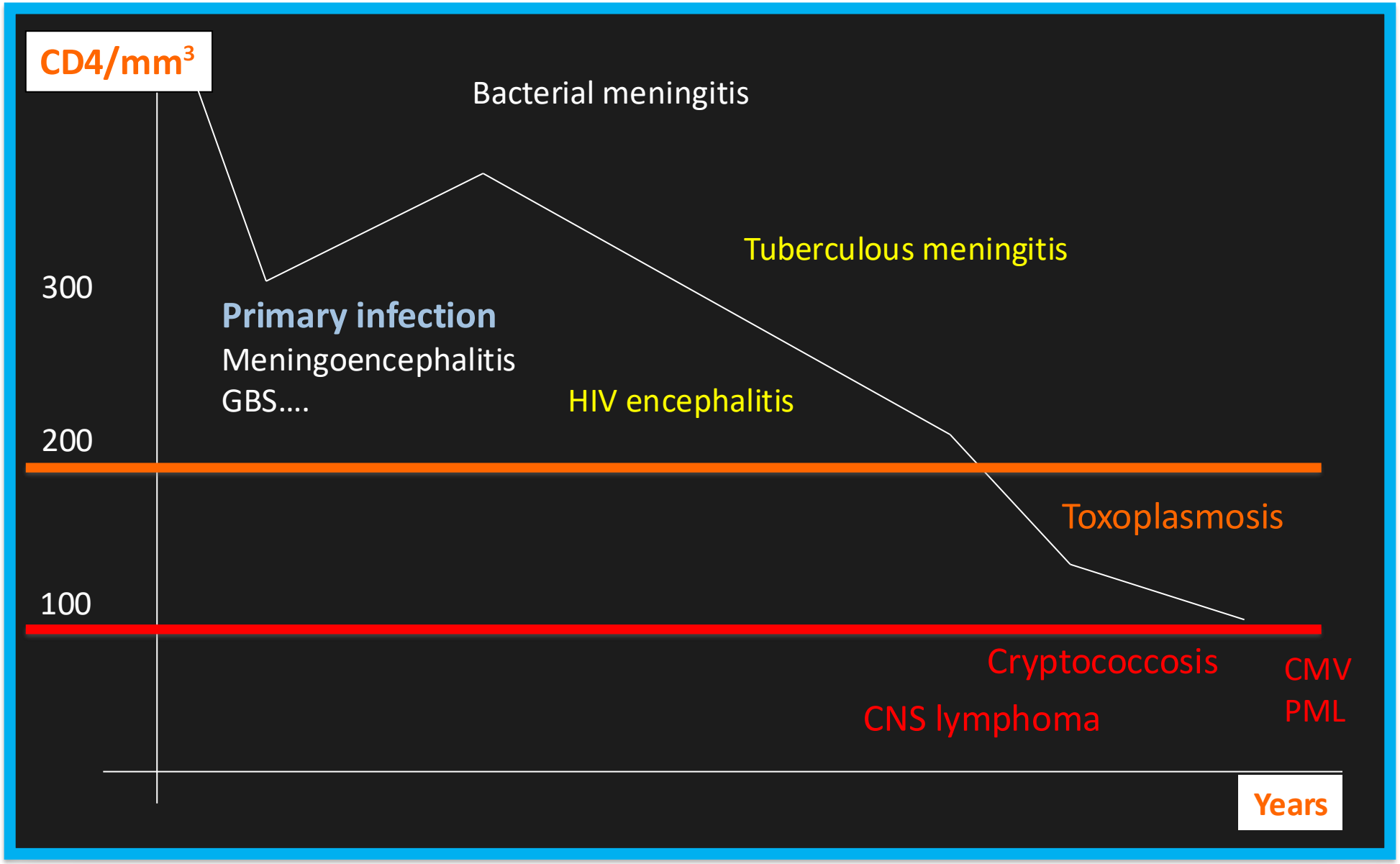
EARLY POSTTRANPLANT SYNDROMES
6 months
CNS infections

LATE POSTTRANSPLANT CNS SYNDROMES
6 months and beyond
- Disseminated / CNS infections
- Post-transplantation CNS lymphoma

TIMELINE OF CNS PROCESSES

AJ Wright and JA Fishman, Clin Inf Dis 2014

HIV infection natural history ….




NE TRAVERSEZ PAS
sans REGARDER dans les
DEUX DIRECTIONS
Un train peut en
CACHER un autre

Urgences Neurologiques chez l'Immunodéprimé

1. Une évaluation multimodale rapide
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CURRENT OPINION

Critical care management of meningitis and encephalitis: an update

Michael Thy[a,b,c], Augustin Gaudemer[d], Geoffroy Vellieux[e,f] and Romain Sonneville[a,g]

Multimodal approach to diagnosis of encephalitis

Medical History

Recent illness ?

Immunosuppression

Seasonal/epidemic context ?

Recent travel ?

Contacts (animals/insects)

Vaccination(s)

Clinical Examination

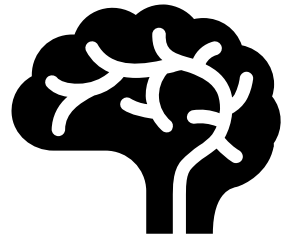
Neurological exam.

Optic nerve exam.

Extra-neurological signs

Brain Imaging

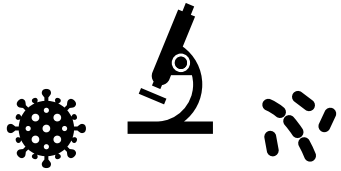
EEG



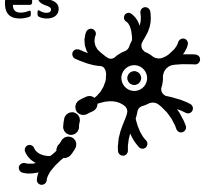
CSF

Serum

Biological Studies



Cultures, PCR, NGS



Immunology tests

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Current Opinion in Critical Care 2022

Critical care management of infectious meningitis and encephalitis

Geert Meyfroidt[1,2*], Pedro Kurtz[3] and Romain Sonneville[4,5]

Table 2 Interpretation of cerebrospinal fluid (CSF) findings

	Normal	Bacterial	Viral	Tuberculous	Fungal
Opening pressure	6–20 cmH_2O	20–50 cmH_2O	6–30 cmH_2O	20–40 cmH_2O	20–100 cmH_2O
Colour	Clear	Cloudy	"Gin" clear	Cloudy/yellow	Clear/cloudy
Cells	< 5/mm^3	High-very high > 1000/mm^3	Slightly increased 10–1000/mm^3	Slightly increased 10–1000/mm^3	Normal-high 0–1000/mm^3
Differential	Lymphocytes	Neutrophils	Lymphocytes	Lymphocytes	Lymphocytes
CSF/blood glucose ratio	50–66%	Low < 40%	Normal	Low-very low < 30–40%	Normal-low
Protein level	< 0.45 g/l	> 1 g/l	0.5–1 g/l	1–5 g/l	0.5–5 g/l

Adapted from [37] and [57]

When performing a lumbar puncture for CSF sampling, the following should be observed:

The minimum amount of CSF sampled must be 120 drops (1 drop amounts to approximately 50 µL): 20 drops (1 mL) for biochemistry tests and 80–100 drops (4–5 mL) for microbiological and virological tests

Part of the CSF must be kept (at + 4 °C and then, if possible, at − 80 °C) for additional biological tests (including tuberculosis diagnostic test)

CSF glucose level must imperatively be combined with a concomitant blood glucose level test

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Intensive Care Medicine 2019

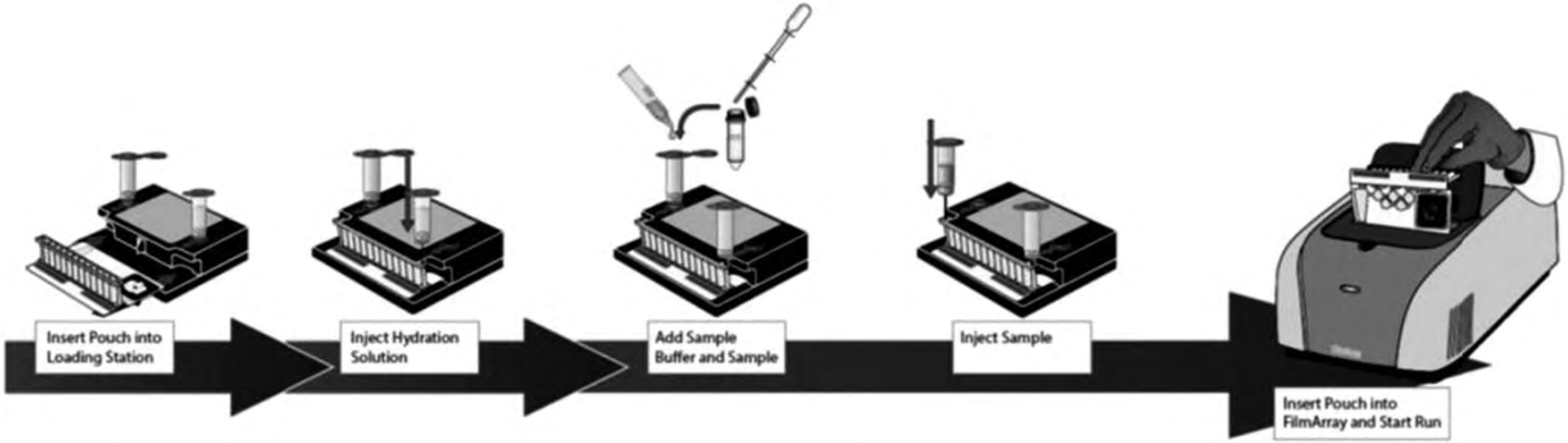
Original Investigation | Critical Care Medicine

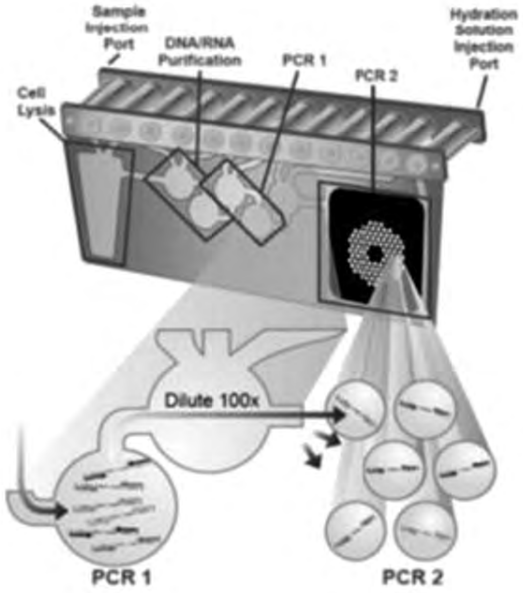
Outcomes of Critically Ill Adult Patients With Acute Encephalitis

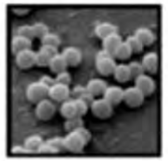
Romain Sonneville, MD, PhD; Camille Couffignal, PharmD, PhD; Bertrand Souweine, MD, PhD; Suela Demiri, MD; Nicolas Terzi, MD, PhD; Fabrice Bruneel, MD; Armand Mekontso Dessap, MD, PhD; Maelle Martin, MD; Clémence Marois, MD; Pierre Bailly, MD; Achille Kouatchet, MD; Guillaume Voiriot, MD, PhD; Florian Reizine, MD; Sarah Benghanem, MD, PhD; Guillaume Louis, MD; Marie Conrad, MD; Sami Hraiech, MD, PhD; Arnaud W. Thille, MD, PhD; Jean-Christophe Navellou, MD; Damien Contou, MD; Simon Bourcier, MD; Marc Tran, MD; Frederic Dailler, MD; Laurent Argaud, MD, PhD; Charles Cerf, MD; Bertrand Guidet, MD, PhD; Damien Roux, MD, PhD; Lionel Kerhuel, MD; Guillaume Van Der Meersch, MD; Saad Nseir, MD, PhD; Adrien Joseph, MD, PhD; Daniel Da Silva, MD; Pascal Beuret, MD, PhD; Benjamine Sarton, MD, PhD; Candice Estellat, MD, PhD; Virginie Godard, PhD; Jérôme Honnorat, MD, PhD; Philippa Catherine Lavallée, MD, PhD; Marina Esposito-Farèse, BS, PhD; Jean-François Timsit, MD, PhD; for the ENCEPHALITICA Investigator Study Group

Table 2. Causes of Encephalitis

Encephalitis cause	Participants, No. (%)		
	Total (N = 310)	Immunocompetent (n = 236)	Immunocompromised (n = 74)
Infectious			
Overall	123 (39.6)	80 (33.9)	43 (58.1)
Herpes simplex virus 1	33 (10.6)	26 (11.0)	7 (9.5)
Varicella zoster virus	15 (4.8)	10 (4.2)	5 (6.8)
Mycobacterium tuberculosis	10 (3.2)	9 (3.8)	1 (1.4)
Listeria monocytogenes	4 (1.3)	3 (1.3)	1 (1.4)
Other infectious[a]	61 (19.7)	32 (13.5)	29 (39.2)
Autoimmune			
Overall	42 (13.5)	38 (16.1)	4 (5.4)
Anti-NMDAR	8 (3.2)	8 (3.4)	0
Acute disseminated encephalomyelitis	4 (1.3)	3 (1.3)	1 (1.4)
Other autoimmune[b]	30 (9.7)	27 (11.4)	3 (4.1)
Other causes[c]	37 (11.9)	29 (12.3)	8 (10.8)
Unknown origin	108 (34.8)	89 (37.7)	19 (25.7)

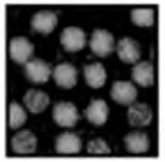






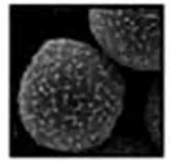
Bacteria

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

Fig. 1. The FilmArray multiplex PCR system.

14 pathogens
in 1 hour

J. Rhein, Diagn Microbiol Infect Dis 2015

CNS infections in the SOT patient

CNS Condition	Approximate Incidence[a]	Usual Posttransplant Onset
Infectious		
Aspergillus species	0.2%	Median 6 mo
Cryptococcus	0.1%	Median 19 mo
Endemic fungi	0.2%	Median 12 mo
Nocardia species	<0.01%	N/A
Progressive multifocal leukoencephalopathy (JC virus)	Up to 0.03%	Mean 1 y
Other molds including Mucorales	0.04%	Median 12 mo

AJ Wright, Clin Inf Dis 2014

Central Nervous System Infections in Heart Transplant Recipients

	1968-1978	1980-1987	1988-2006	TOTAL	
Patients	N=182	N=417	N=315	N=914	%
CNS infections	27	13	8	**48**	**5%**
Aspergillus	10	3	1	14	<2%
C. neoformans	5	1	3	9	<1%
Listeria	4	2	0	6	<1%
Toxoplasmosis	4	2	0	6	<1%
JC virus	0	1	2	3	<1%
VZV	0	0	2	2	<1%
Nocardia	0	2	0	2	<1%

All patients developed their first symptoms within 4 years of HT
(Half within 1 year after transplantation)

D Van de Beek, Arch Neurol 2007

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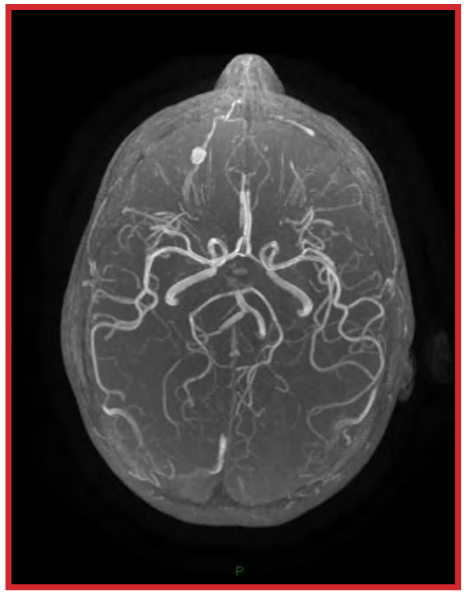
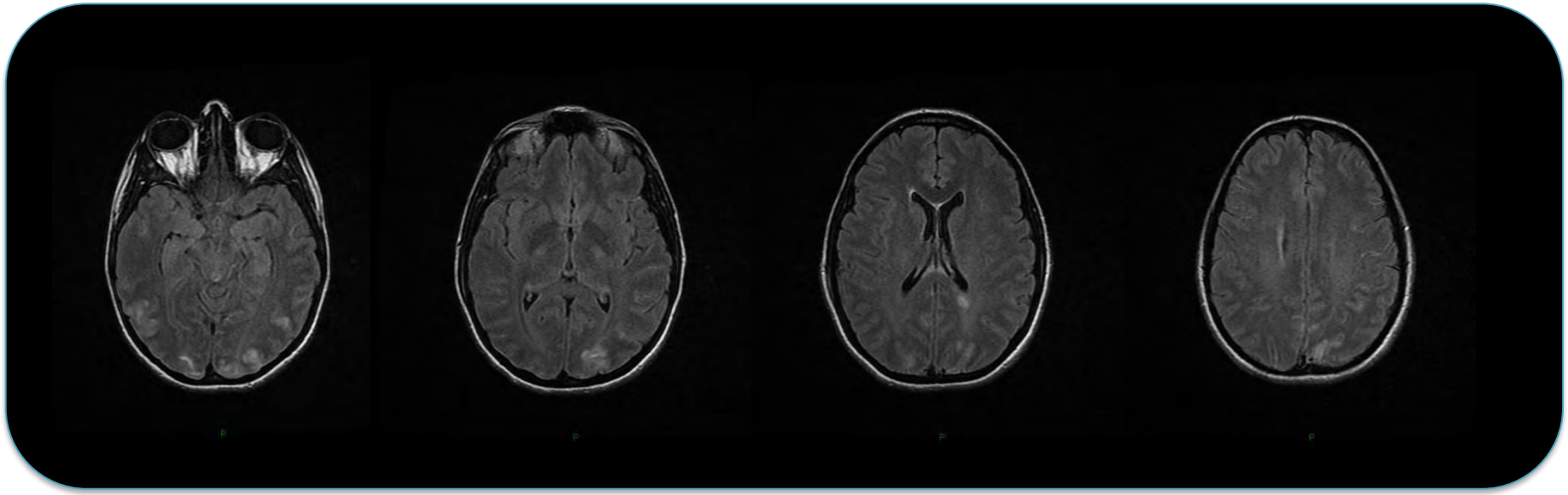
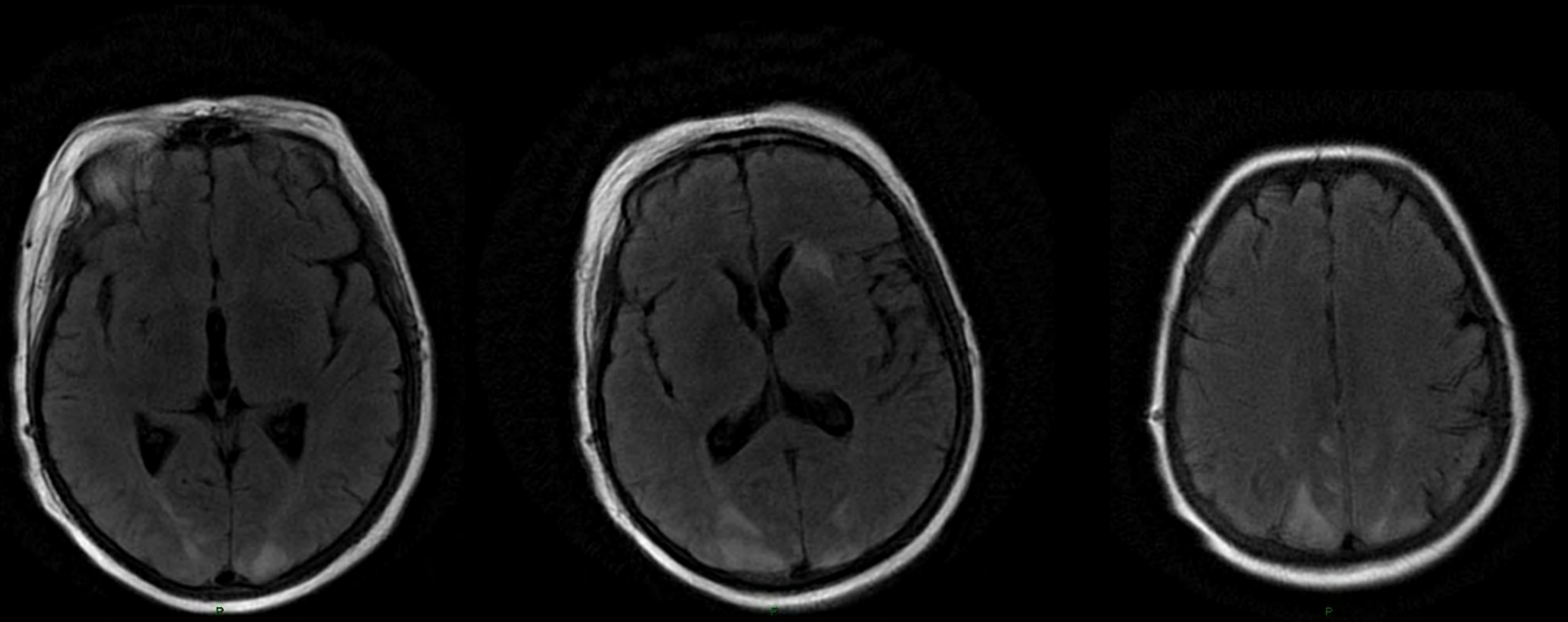
- Transplantée cardiaque (CM du post-partum) en avril 2023
- Ttt : corticoides, ciclosporine, mycophénolate
- à 2 mois de la TC : ralentissement psychomoteur sur qq jours
  - Convulsions « inaugurales » + coma post-critique
  - GCS 13
  - Pas de signe focal
  - 37.8° C
  - PA 140/80 mmHg FC 80

?







IRM : “oedème vasogénique”

LCR : cell 2/mm^3, prot 0.6 g/l, glucose 4 mmol/l, GRAM-, encre de chine -, mPCR -, culture -

494 THE NEW ENGLAND JOURNAL OF MEDICINE Feb. 22, 1996

A REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME

JUDY HINCHEY, M.D., CLAUDIA CHAVES, M.D., BARBARA APPIGNANI, M.D., JOAN BREEN, M.D., LINDA PAO, M.D., ANNABEL WANG, M.D., MICHAEL S. PESSIN, M.D., CATHERINE LAMY, M.D., JEAN-LOUIS MAS, M.D., AND LOUIS R. CAPLAN, M.D.

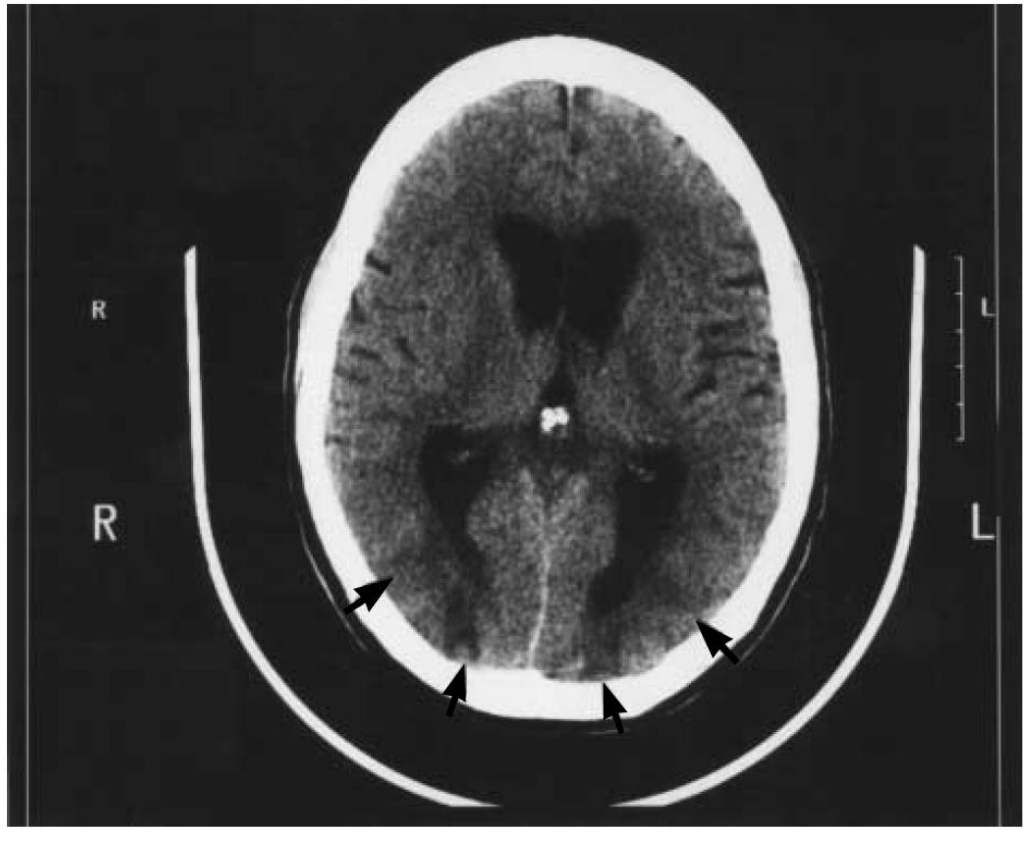
15 patients hospitalized for acute illness

Immunosuppressive therapy (50%)

Reversible syndrome of
- headache
- altered mental functioning
- Seizures
- Loss of vision

Abrupt increases in blood pressure

Renal impairment



Posterior leukoencephalopathy

New Eng J Med 1996

A REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME

JUDY HINCHEY, M.D., CLAUDIA CHAVES, M.D., BARBARA APPIGNANI, M.D., JOAN BREEN, M.D., LINDA PAO, M.D., ANNABEL WANG, M.D., MICHAEL S. PESSIN, M.D., CATHERINE LAMY, M.D., JEAN-LOUIS MAS, M.D., AND LOUIS R. CAPLAN, M.D.

PATIENT NO.	AGE (YR)/ SEX	DIAGNOSIS OR DRUG TREATMENT	CLINICAL FINDINGS	HIGHEST BLOOD PRESSURE	LESIONS ON CT OR MRI	HIGHEST SERUM CREATININE LEVEL*
				mm Hg		*mg/dl*
1	30/F	Systemic lupus erythematosus, hypertensive encephalopathy	Hypertension, headache, lethargy, vomiting, cortical blindness	200/110	Occipital lobe (bilateral), posterior parietal lobe (bilateral), posterior temporal lobe (right), frontal lobe (left), thalamus (right)	3.3
2	61/F	Acute nephritis, hypertensive encephalopathy	Hypertension, headache, vomiting, seizures, cortical blindness, confusion	200/100	Occipital lobe (bilateral), posterior temporal lobe (bilateral), posterior parietal lobe (bilateral)	3.9
3	27/M	Hepatorenal syndrome, hypertensive encephalopathy	Headache, vomiting, hypertension, visual hallucinations, confusion, cortical blindness	180/110	Occipital lobe (bilateral), posterior parietal lobe (right), frontal lobe (bilateral), posterior temporal lobe (right)	16.1
4	39/F	Systemic lupus erythematosus, hypertensive encephalopathy	Headache, seizures, hypertension, vomiting, confusion, right hemianopia	200/130	Occipital lobe (left), posterior parietal lobe (bilateral), posterior temporal lobe (left), frontal lobe (left), pons (left)	3.1
5	25/F	Puerperal eclampsia	Headache, hypertension, vomiting, seizures, visual neglect, right hemiparesis	170/100	Occipital lobe (bilateral), posterior parietal lobe (right), posterior temporal lobe (left), caudate (right)	0.9
6	15/F	Puerperal eclampsia	Headache, nausea, hypertension, seizures, left hemiparesis	150/104	Occipital lobe (bilateral), posterior parietal lobe (right)	0.4
7	28/F	Puerperal eclampsia	Headache, lethargy, vomiting, seizures, hypertension, visual blurring, left hemiparesis	160/100	Occipital lobe (bilateral), parietal lobe (bilateral), frontal lobe (bilateral)	0.1
8	62/F	Liver transplantation, treatment with cyclosporine	Hypertension, seizures, cortical blindness	142/95	Occipital lobe (bilateral), posterior temporal lobe (right), parietal lobe (bilateral)	2.7
9	47/F	Aplastic anemia, treatment with cyclosporine	Headache, hypertension, vomiting, seizures, cortical blindness	180/88	Occipital lobe (bilateral), posterior parietal lobe (bilateral), posterior temporal lobe (left)	1.5
10	47/F	Bone marrow transplantation, treatment with cyclosporine	Hypertension, seizures, lethargy, left hemianopia	150/80	Occipital lobe (bilateral), posterior temporal lobe (bilateral)	2.3
11	36/F	Renal transplantation, treatment with cyclosporine	Hypertension, seizures, confusion	210/110	Occipital lobe (bilateral), parietal lobe (bilateral), frontal lobe (bilateral)	5.3
12	50/M	Melanoma, treatment with interferon alfa	Hypertension, dizziness, status epilepticus, left hemiparesis, left hemianopia, bilateral dysmetria, lethargy	180/110	Occipital lobe (bilateral), posterior parietal lobe (right), cerebellum (bilateral)	0.9
13	48/F	Liver transplantation, treatment with tacrolimus	Abulia, left hemiparesis, dystonia of right arm	100/60	Frontal lobe (right), internal capsule (left), central white matter (bilateral)	0.7
14	20/F	Liver transplantation, treatment with tacrolimus	Lethargy, asterixis, seizure	120/80	Occipital lobe (bilateral), posterior temporal lobe (left), posterior parietal lobe (left), frontal lobe (left), centrum semiovale (bilateral)	1.2
15	57/F	Liver transplantation, treatment with tacrolimus	Lethargy, asterixis	130/80	Occipital lobe (bilateral), posterior parietal lobe (bilateral), pons	0.9

*To convert values for creatinine to micromoles per liter, multiply by 88.4.

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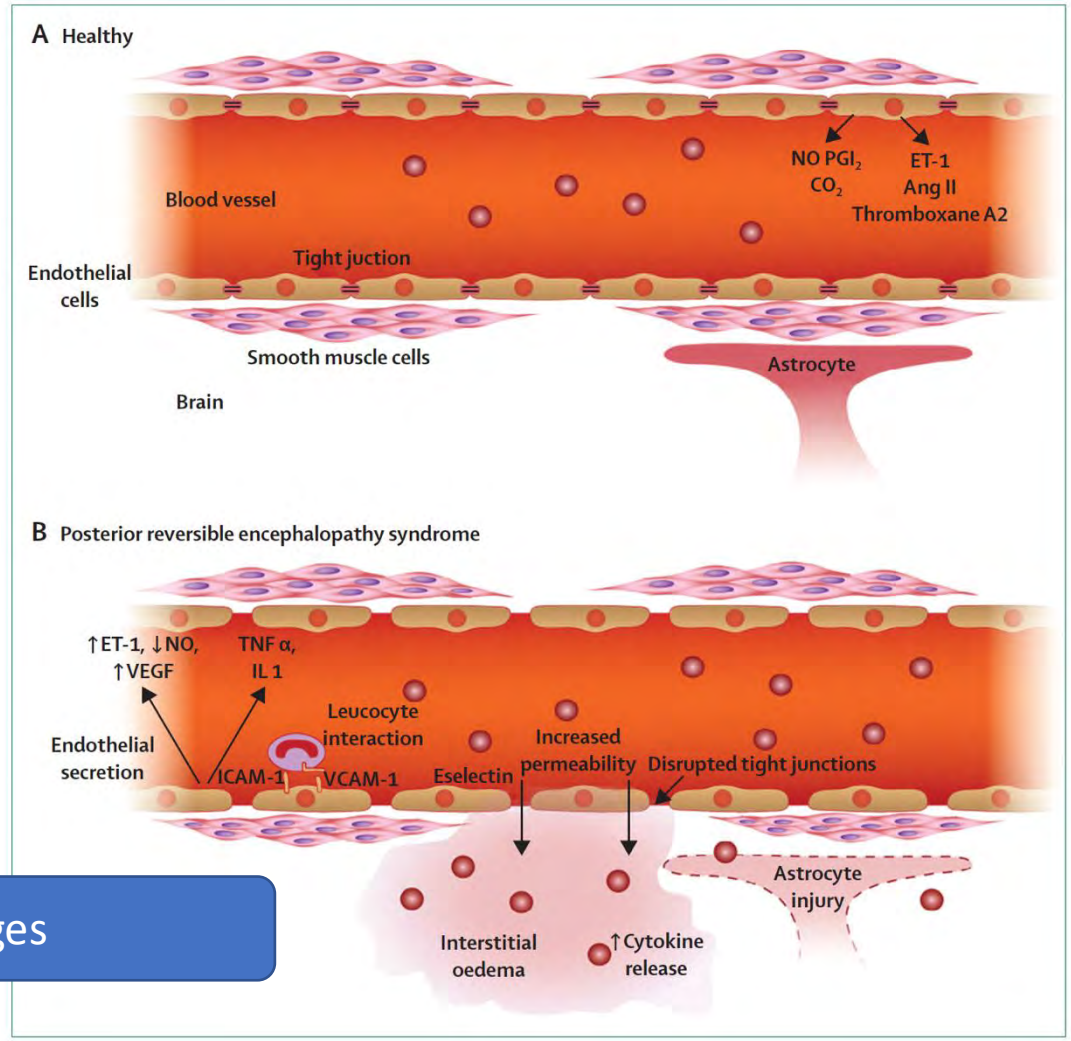
New Eng J Med 1996

PRES pathophysiology

Endothelial dysfunction (circulating cytokines)

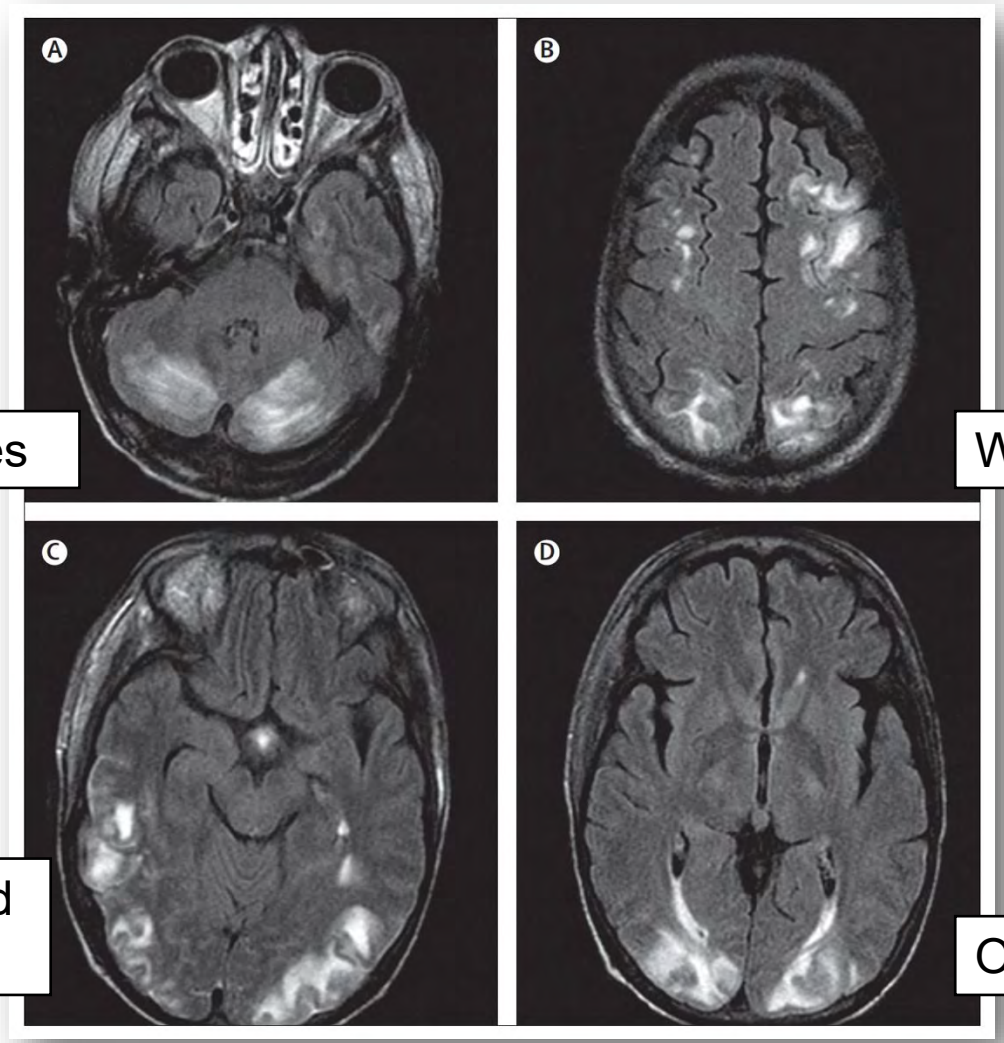
Abrupt BP changes



Lancet Neurol 2015

Typical MRI findings in PRES

Axial T2 FLAIR sequences show predominantly subcortical abnormal T2 signal bilaterally



Cerebral hemispheres

Watershed regions

Posterior parietal and temporal lesions

Occipital lesions

Lancet Neurol 2015

Proposed algorithm for the diagnosis of PRES

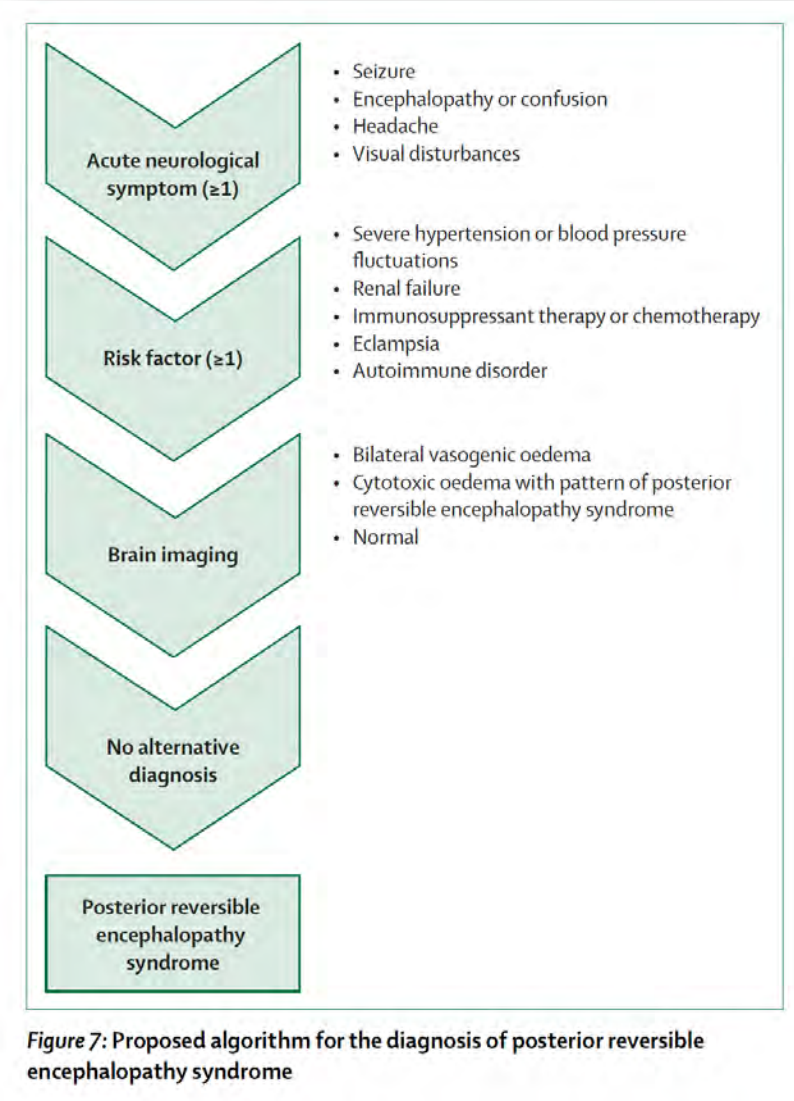
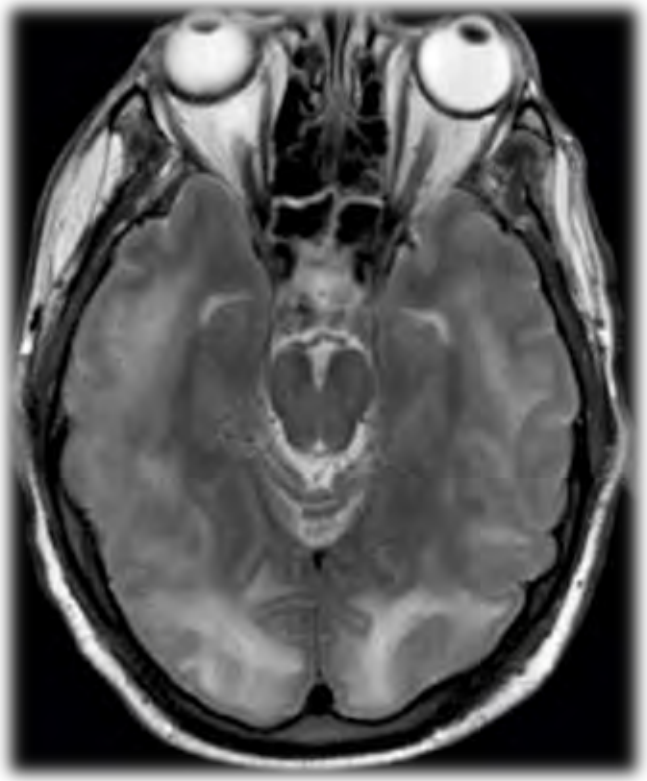


Figure 7: **Proposed algorithm for the diagnosis of posterior reversible encephalopathy syndrome**

Principes de prise en charge du PRES



- **Pas de traitement spécifique**

- Identifier et corriger **facteur déclenchant**

(pathologie systémique, toxicité médicament)

- **Ttt antihypertenseur si PAS > 160 mm Hg**

(pas d'étude spécifique pour le PRES)

=> Objectif de réduction relative de **25%** dans les premières heures)

- **Antiepileptiques si crises**

(pas d'étude spécifique pour le PRES)

Posterior Reversible Encephalopathy Syndrome

Romergryko G. Geocadin, M.D.

Table 2. Drugs and Toxic Agents Related to PRES.*

Drug Class or Exposure	Specific Drugs and Toxic Agents
Chemotherapeutic drugs	Bevacizumab, tyrosine kinase inhibitors, bortezomib, cytarabine, gemcitabine, L-asparaginase, methotrexate, vincristine, and cisplatin (platinum-based agents)
Immune-modifying drugs	Tacrolimus, sirolimus, cyclosporine A, rituximab, interleukin, tumor necrosis factor antagonist, and interferon alfa
Pharmacologic agents	Erythropoietin, granulocyte colony-stimulating factor, voriconazole, butalbital–acetaminophen–caffeine therapy, pseudoephedrine, and antiretroviral therapy for human immunodeficiency virus infection
Intoxications and exposures	Alcohol intoxication, drug overdose (e.g., lithium, dextroamphetamine, acetaminophen, ephedrine, phenylpropanolamine, digitoxin, bismuth), chemical substance (e.g., organophosphates), illicit drugs (e.g., cocaine, amphetamine, mephedrone, kratom, amide of lysergic acid), and natural toxins (e.g., from snake bites, scorpion bites, wasp stings, mushrooms, licorice)

* These examples do not represent a full listing of drugs and toxic agents related to PRES.

New Eng J Med 2023

Urgences Neurologiques chez l'Immunodéprimé

1. Une évaluation multimodale rapide
2. Eliminer infection(s) du SNC
3. PRES ?
4. Autre neurotoxicité ?
5. Conclusion

Neurotoxicité chez l'immunodéprimé ?

TABLEAU CLINIQUE COMPATIBLE

- Sd confusionnel – coma
- +/- myoclonies
- +/- convulsions
- Pas de signe focal

- IRM "normale"
- PL "normale"

- EEG ?

NEUROTOXIQUE(S)

- Benzodiazepines
- Beta-lactamines
  - Céfépime
  - Imipénème
  - …

- Voriconazole
- CNIs
- …

+/- DOSAGE TOXICOLOGIQUE ?

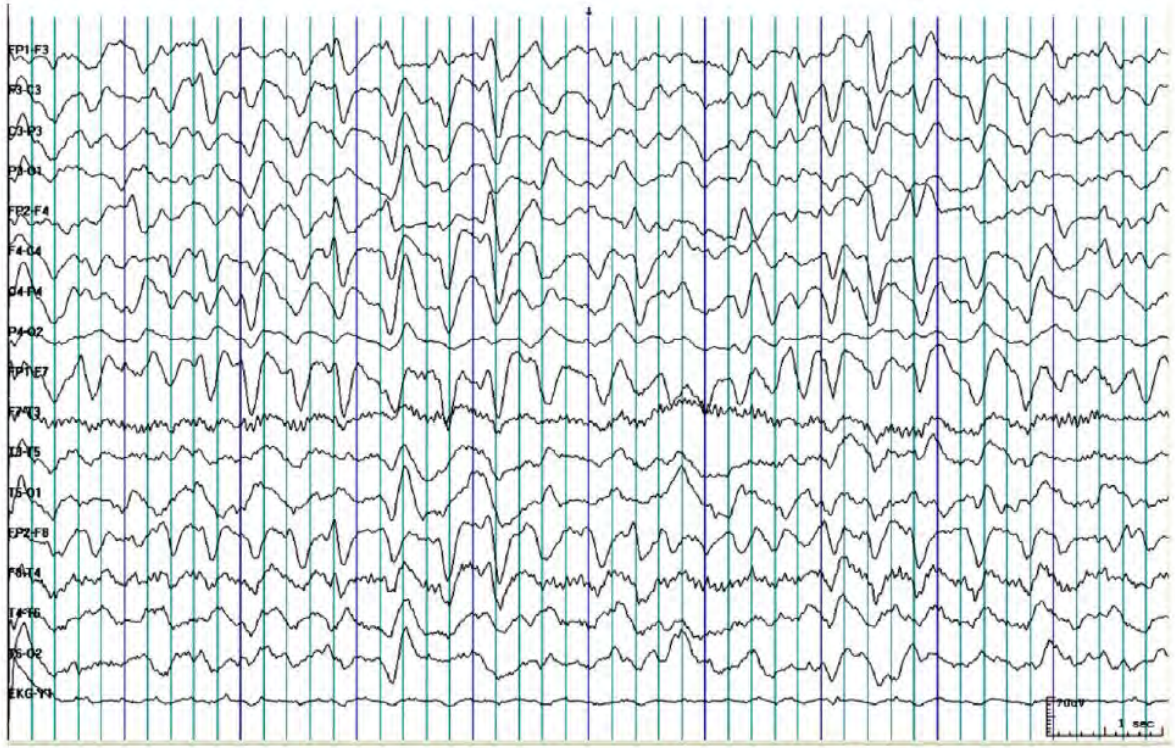
RÉSOLUTION DES SYMPTOMES À L'ARRÊT DU MEDICAMENT EN CAUSE

Université Paris Cité | Hôpital Bichat Claude-Bernard AP-HP | iame RESEARCH CENTER ON INFECTIOUS DISEASES

Significance of triphasic waves in patients with acute encephalopathy: A nine-year cohort study ☆

Raoul Sutter [a,b,c,e,*], Robert D. Stevens [a,b,c,d,e], Peter W. Kaplan [b,e]

Triphasic waves (TWs)
a frequent EEG finding in ICU patients



Frequent and high-voltage (>100 microV) TWs
Fronto-parietal predominance

Multifactorial origin

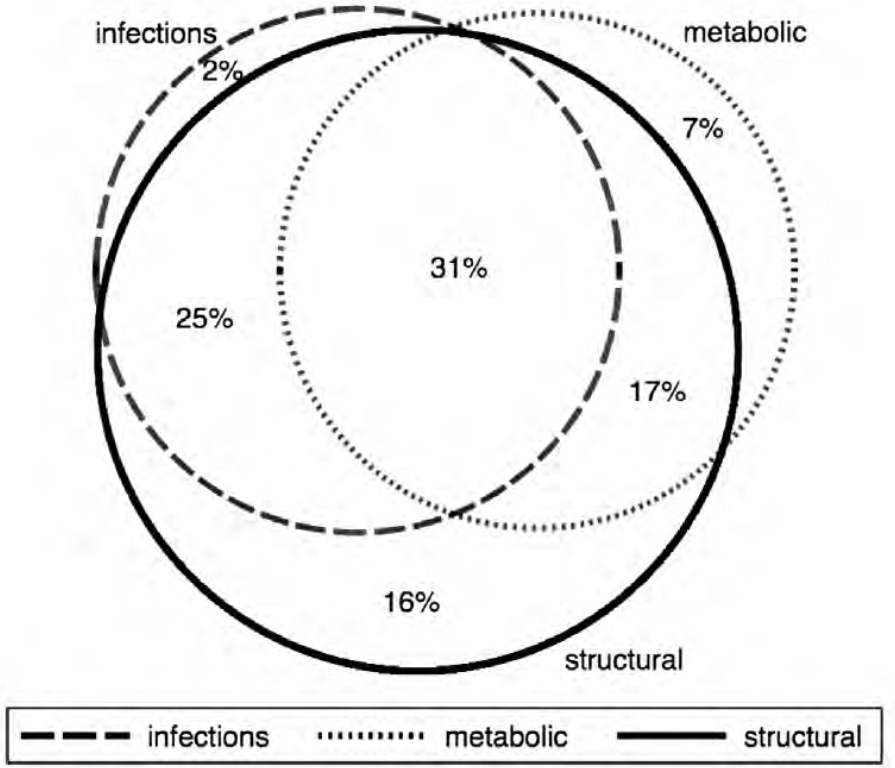


Fig. 2. Proportional distribution of infections, metabolic derangements and structural brain abnormalities in encephalopathic patients with triphasic waves.

Clin Neurophysiol 2013

RESEARCH Open Access

Cefepime-induced neurotoxicity: a systematic review

Lauren E. Payne[1*], David J. Gagnon[2], Richard R. Riker[3], David B. Seder[3], Elizabeth K. Glisic[2], Jane G. Morris[4] and Gilles L. Fraser[5]

Diagnostic clues

+/- Risk factors for betalactam neurotoxicity

Acute neurologic presentation
- Encephalopathy
- Myoclonus
- Seizure

+/- abnormal EEG patterns
- Triphasic waves
- Non-convulsive SE
- Diffuse slowing
- PEDs

+/- Elevated drug concentrations

Drug concentrations, mg/L	
Median serum, n = 21 (range)	45 (15–284)
Median trough, n = 13 (range)	38 (15–224)
Median CSF, n = 4 (range)	13 (6–18)
Median for appropriately dosed patients, n = 7 (range)	60 (22–74)
Median for inappropriately dosed patients, n = 10 (range)	39 (15–284)
Trough for appropriately dosed patients, n = 6 (range)	54 L (37–65)
Median onset of neurotoxic effects (IQR), days	4 (2–6)

CNS central nervous system
[a]No patients were treated for meningitis/CNS infections

Treatments

Cefepime discontinuation

Cefepime-free interval w/dose reduction

Hemodialysis ?

Benzodiazepine for seizure activity ?

Improvement after cefepime discontinuation !

Crit Care 2017

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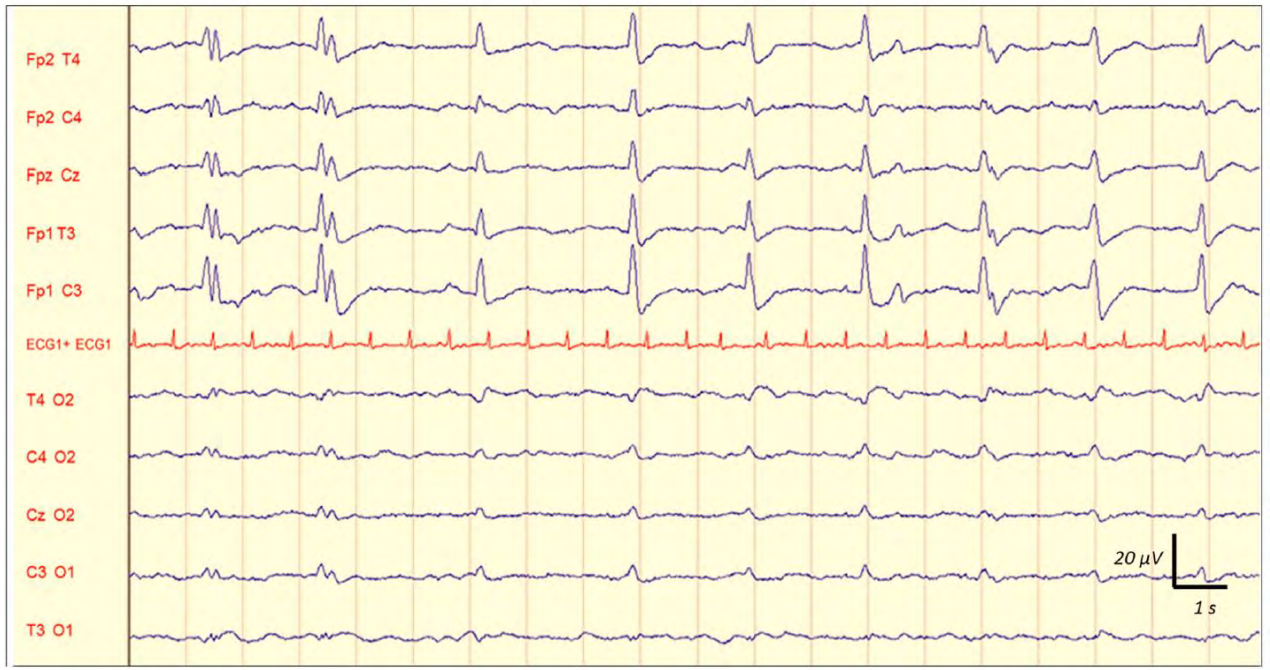
Risque de récidive de crise ?

4 CRITERES

- Absence de lésion structurelle
- Pas de trouble métabolique
- Pas de ttt neurotoxique résiduel
- EEG inter-critique « normal »



Si 4 critères +
=> Antiépileptique au long cours ne sont PAS NECESSAIRES

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EF Wijdicks, Neurologic complications of organ transplantation, 2009

Urgences Neurologiques chez l'Immunodéprimé

1. Une évaluation multimodale **rapide**
2. Une **approche syndromique**
3. Penser aux **causes multiples** !
4. Les **complications** neurologiques **métaboliques / toxiques** sont précoces et fréquentes et souvent de bon pronostic
5. Les **infections du SNC** sont plus rares, plus tardives et souvent plus graves

Merci ☺ !

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