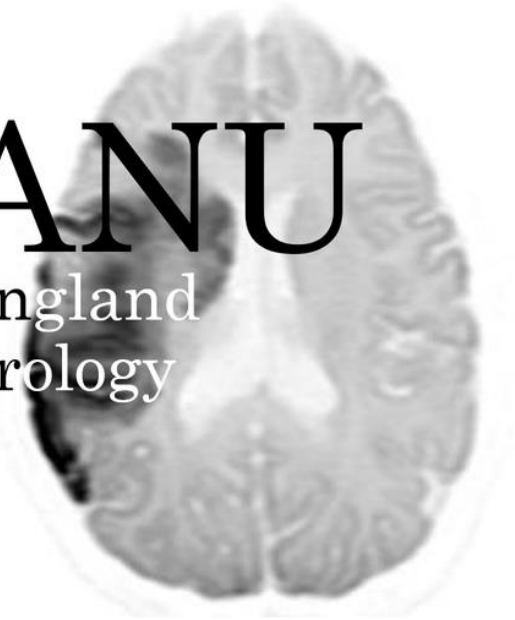
NEANU
North of England
Acute Neurology
Update



Neurological aspects of general medicine

Rajiv Mohanraj

MANCHESTER 1824
The University of Manchester

Manchester Centre for Clinical Neurosciences

Salford Royal NHS
NHS Foundation Trust

Case 1

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Update

- 55 F - GP referral to MAU
- 5 day history of confusion
  - Forgetting PIN / phone numbers
- Speech slurred
- Veering off to the left on walking
- Behaving out of character
  - Standing with hands under cold tap for 45 minutes
  - Appears vacant
  - Slept for 15 hours the previous day

Case 1

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Update

- 3 months previously
  - Tired all the time
  - GP – iron deficiency anaemia – iron sup – ref for endoscopy
- Office worker, lives with mother and sister
- Does not drink alcohol
- Smokes 5 / day

- On examination
  - Temp 35.6
  - O2 sats 100%
  - Crackles and reduced AE right base
  - Speech slow and slurred
  - No neurological deficits
  - Rest NAD

- Diagnosis?
  - Clinical syndrome
  - Possible aetiology

Case 1

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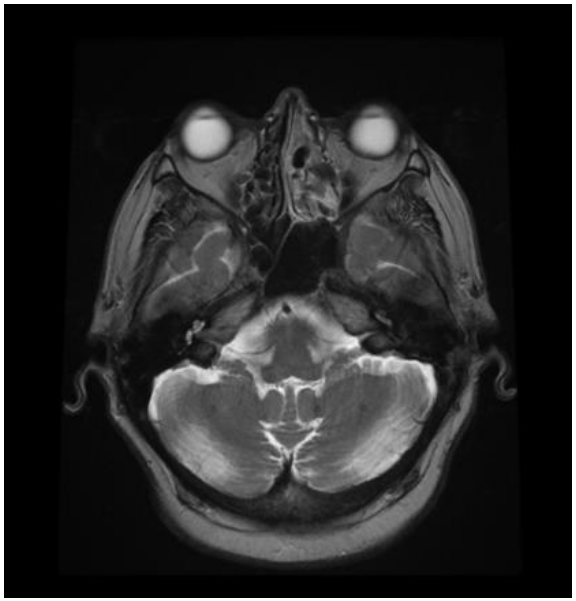
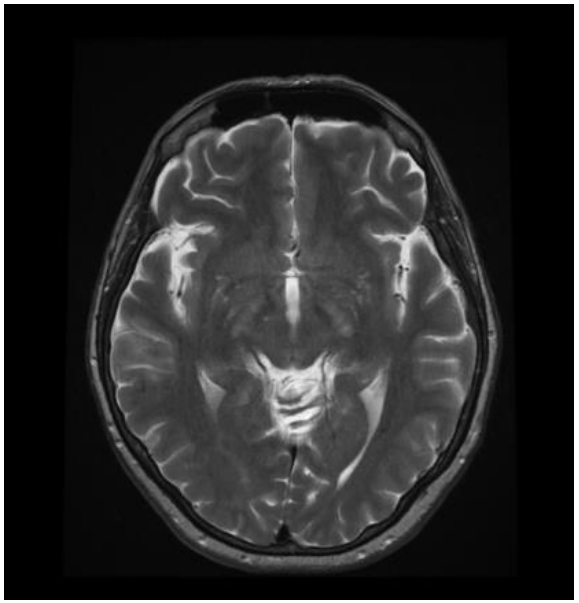
- Diagnosed ?encephalitis , started ceftriaxone and acyclovir
- MRI brain





- LP – WCC <1, RCC 72, Protein 0.47, glucose 6.9
  - Bacterial culture, viral PCR negative
- Discharged after 5 days

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Update

Six months later

Neurology clinic

- Still off work
- Speech slow, word finding difficulty
- Tired, sleeps 2 hours during the day
- Emotionally labile

- MRI unchanged from previous
- VGKC Abs 101, NMDA negative
- Admitted

Neurology ward

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Update

- Able to give good history
- AMT 10/10
- Behaviour appropriate
- normal affect
- Unable to tandem walk
- Otherwise NAD

- Hb 8.8
- U&E, LFTs, TFT, AI screen - negative
- NMDA, TPO Abs negative
- CSF
  - WCC 3
  - RCC 2
  - Protein 0.65
  - Glucose 3.8 (plasma 13.9)

EEG

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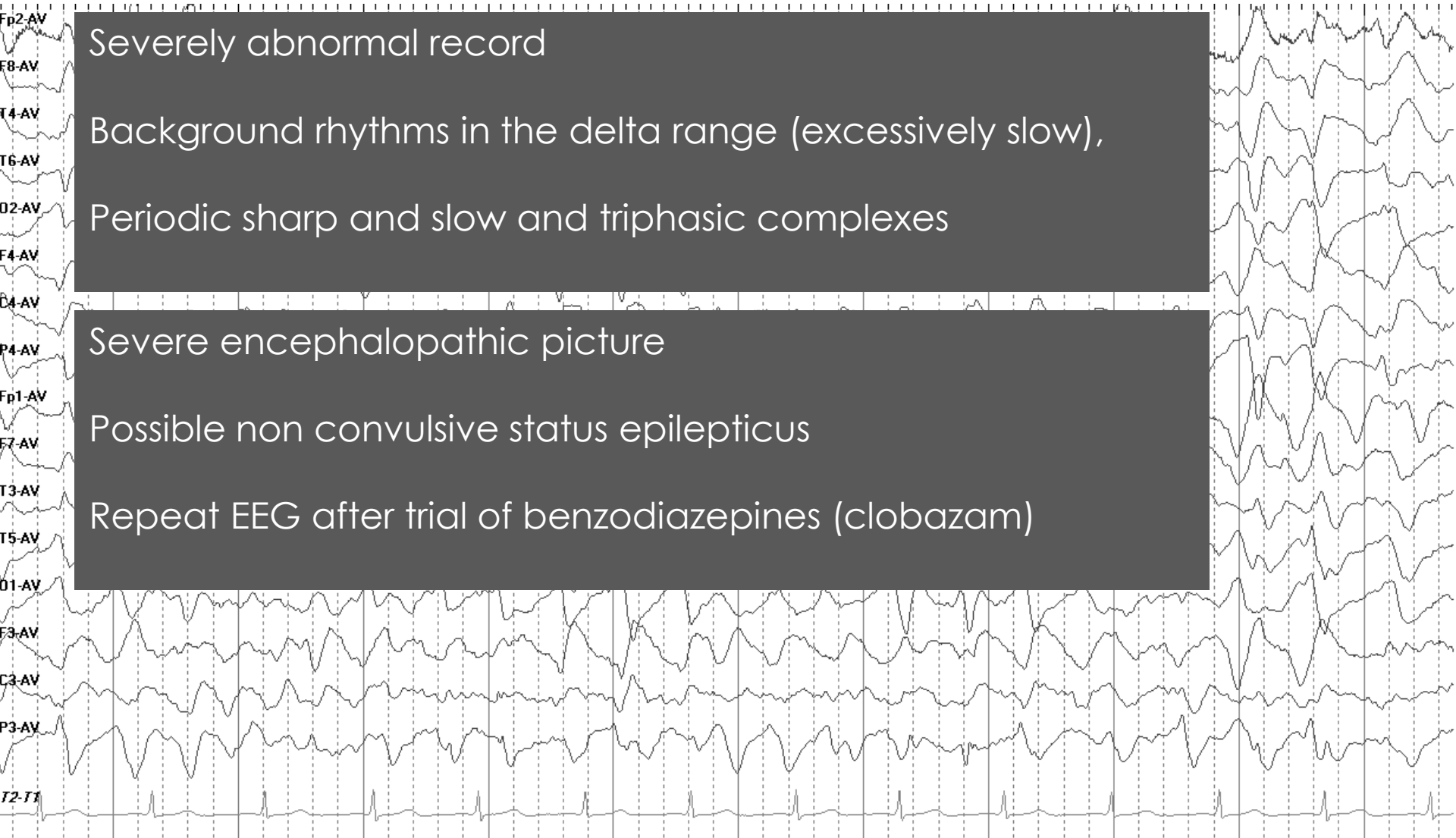

Severely abnormal record

Background rhythms in the delta range (excessively slow),

Periodic sharp and slow and triphasic complexes

Severe encephalopathic picture

Possible non convulsive status epilepticus

Repeat EEG after trial of benzodiazepines (clobazam)

Management

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- Started on Clobazam 10mg BD
  - Extremely drowsy
  - Bed bound
  - Barely able to speak

- Repeat EEG

EEG

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Update

Record still abnormal

Background rhythms in the theta range (slow)

Periods of fast activity and FIRDA

Moderate encephalopathy

EEG improved with clobazam

Repeat study in 1 week recommended

WE ARE MISSING SOMETHING!

Review DGH notes

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Acute Neurology
Update

- Letter from gastroenterology 3 months after admission
  - Referral for investigation of IDA
  - Mentions previous referral in 2014 for 'mildly deranged LFTs'
  - Gastroscopy '3 varices'
  - Started on carvedilol

- Bloods at the time of original admission
  - Hb 79
  - MCV 78
  - Bilirubin 50
  - Albumin 28
  - INR 1.4

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Update

Serum ammonia 110

Diagnosis: Hepatic encephalopathy

Liver biopsy – cirrhosis and macrovesicular steatosis

Hepatic encephalopathy

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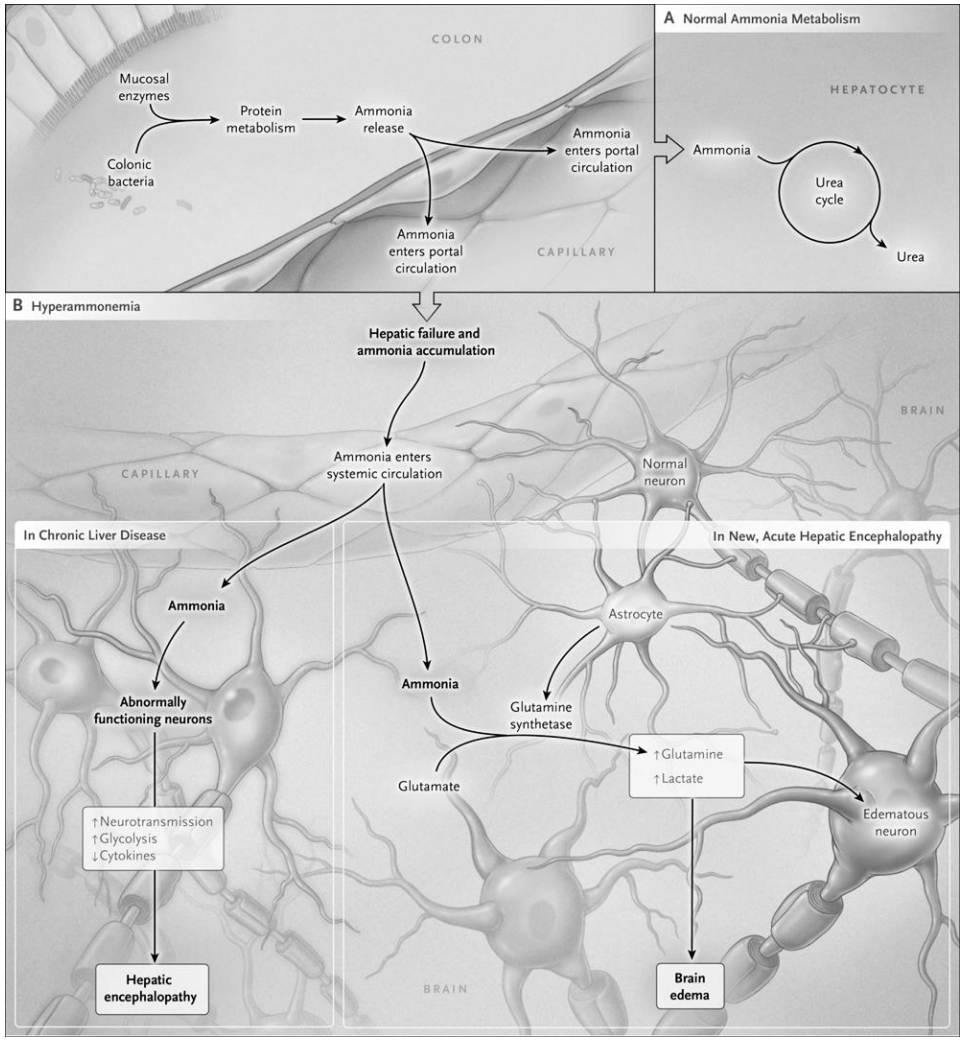
Update



- 30-45% of patients with cirrhosis
  - Up to 70% have subtle HE
- Survival following HE
  - 1 year = 42%
  - 3 years = 23%

Wijdicks, N Engl J Med 2016; 375:1660-70

West Haven criteria for HE

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Update

Grade	Consciousness	Intellect and behaviour	Neurologic findings
0	Normal	Normal	Normal Impaired neuropsych MHE
1	Mild lack of awareness	Reduced attention span	Impaired subtraction Mild asterixis or tremor
2	Lethargic	Disorientation Inappropriate behaviour	Obvious asterixis Slurred speech
3	Somnolent, rousable	Gross disorientation Bizarre behaviour	Rigidity and clonus Hyper-reflexia
4	Coma	Coma	Decerebrate posturing

CNS effects of renal failure

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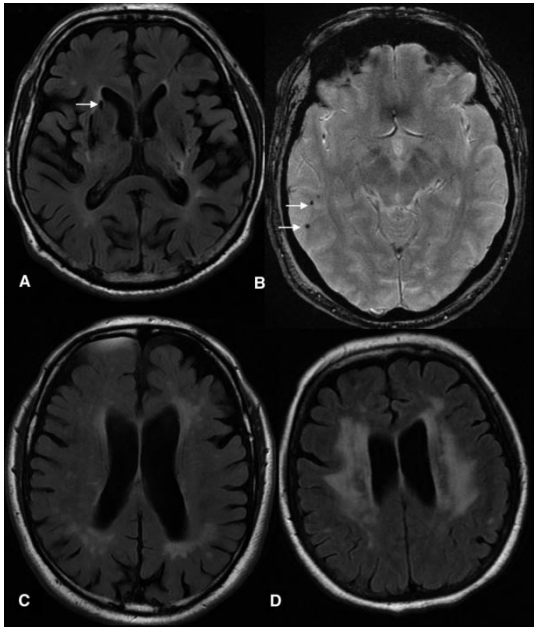
Update

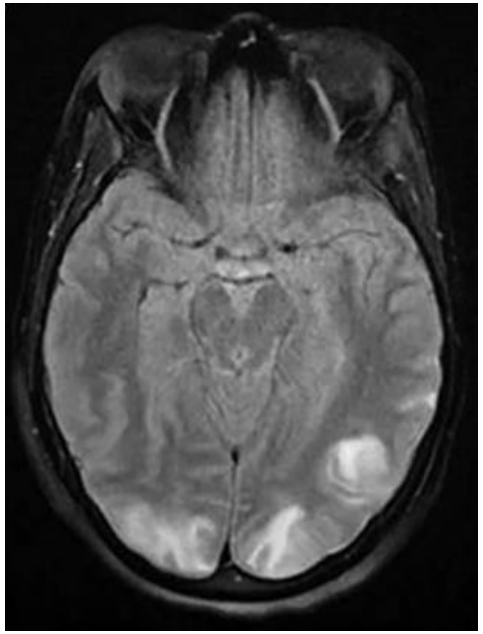
Cognitive disorders

- Encephalopathy
- Dementia



Vascular disorders

- Infarcts
- PRES



Movement disorders

- Tremor
- Dystonia
- Chorea
- Myoclonus

Jabbari B, Vaziri ND. Hemodial Int. 2018; 22: 150-160.

Encephalopathy in respiratory failure

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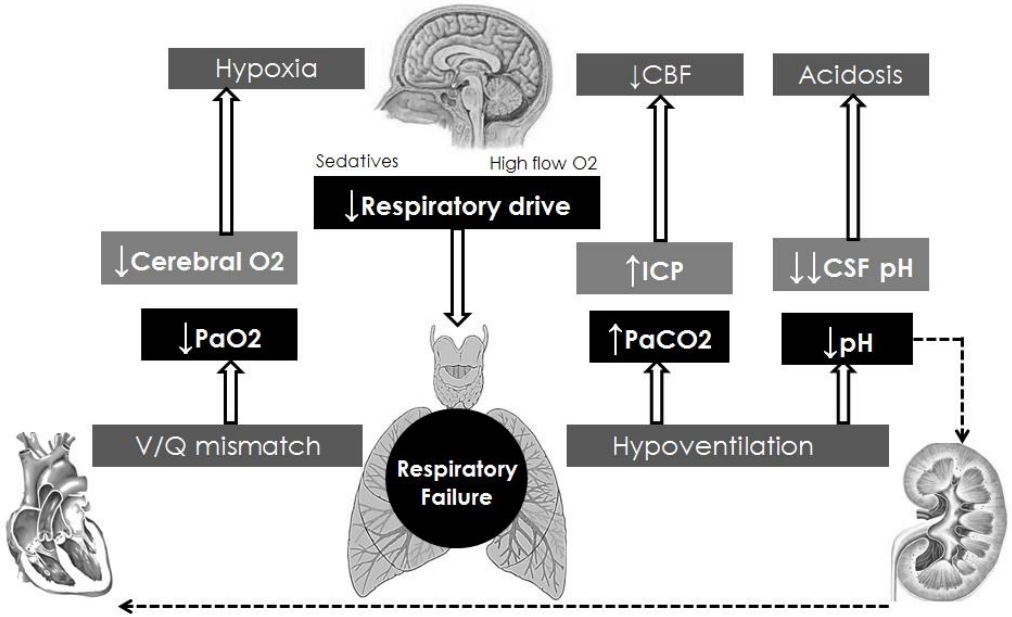
Update



PATIENT

VIDEO

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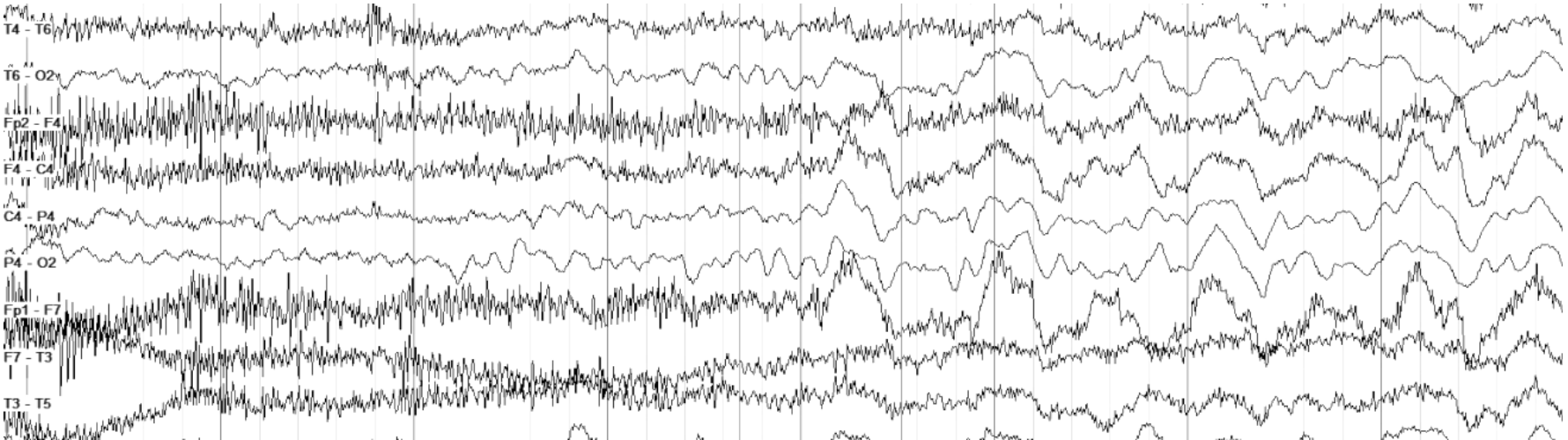

Encephalopathy v encephalitis

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Update

- Encephalopathy
  - Clinical state of altered mental status, ranging from subtle impairment of cognitive function to coma

- Encephalitis
  - Brain inflammation as a consequence of direct infection of the brain parenchyma or autoimmune processes

Diagnostic criteria for Encephalitis

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Acute Neurology
Update

- Major Criterion (required):
  - Altered mental status (decreased or altered level of consciousness, lethargy or personality change) lasting ≥24 h with no alternative cause identified
- Minor Criteria (2 =possible encephalitis; ≥3 =probable /confirmed encephalitis)
  - Fever ≥38° C (100.4°F) within the 72 h before or after presentation
  - Generalized or partial seizures not due to a pre-existing seizure disorder
  - New onset of focal neurologic findings
  - CSF WBC count ≥5/mm3
  - Abnormality of brain parenchyma on imaging suggestive of encephalitis
    - New compared to previous studies or appears acute in onset
  - Abnormality on EEG consistent with encephalitis
    - Not attributable to another cause

Consensus document on encephalitis. Clinical Infectious Diseases 2013;57(8):1114–28

Febrile encephalopathy = encephalitis?

Case 2

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Acute Neurology
Update

- 90 F, nursing home resident
- Admitted with chest infection
  - Febrile
  - Confused
  - CRP 25
- 3 days later
  - Unresponsive
- CT brain – age related atrophy
- LP – CSF protein 0.8, otherwise normal

Case 2

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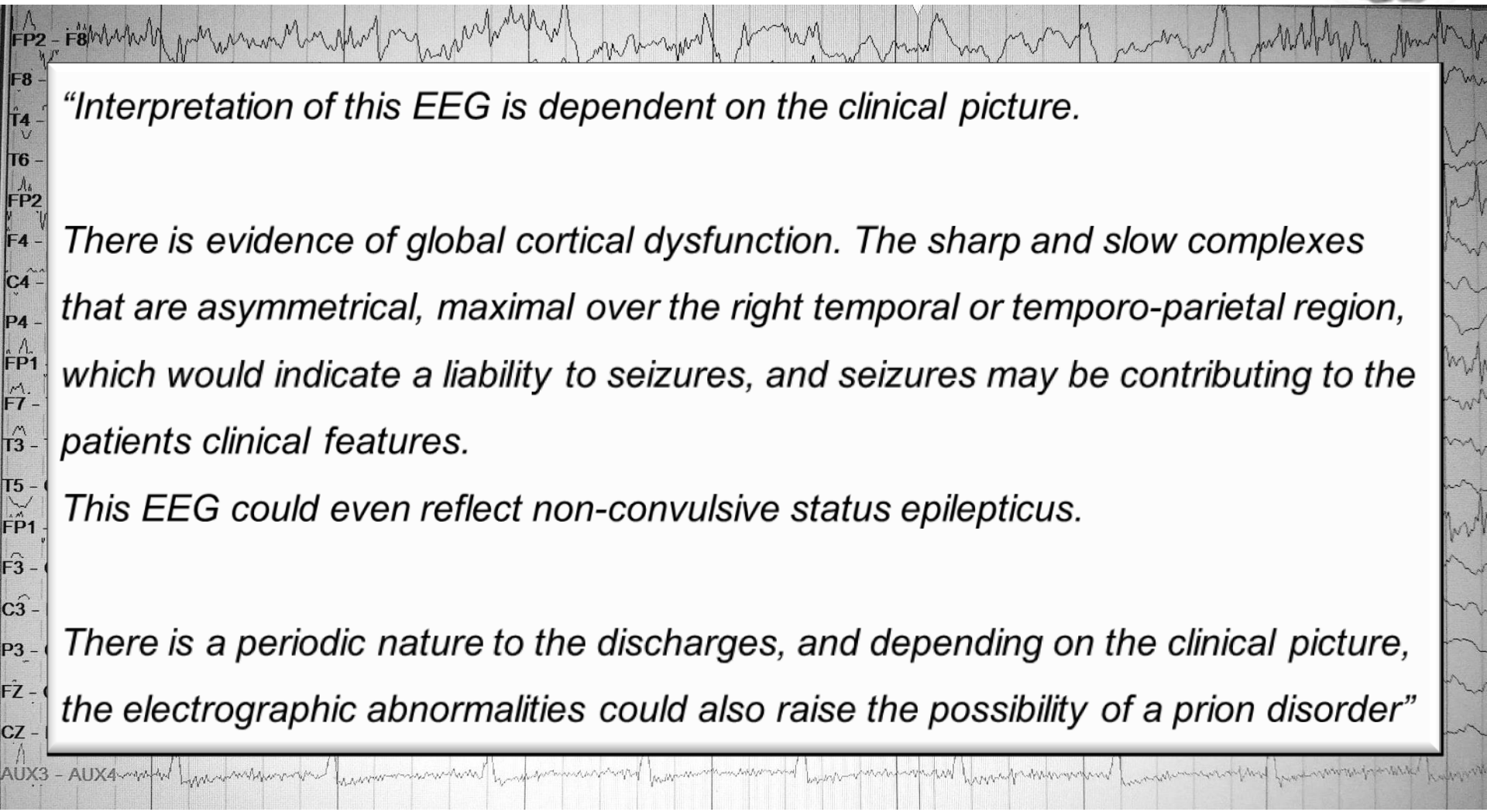
Acute Neurology
Update



"Interpretation of this EEG is dependent on the clinical picture.

There is evidence of global cortical dysfunction. The sharp and slow complexes that are asymmetrical, maximal over the right temporal or temporo-parietal region, which would indicate a liability to seizures, and seizures may be contributing to the patients clinical features.

This EEG could even reflect non-convulsive status epilepticus.

There is a periodic nature to the discharges, and depending on the clinical picture, the electrographic abnormalities could also raise the possibility of a prion disorder"

Case 2

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Update

- Discussed with on call neurology registrar
  - 'We have a 90 year old in non convulsive status'
  - Loaded with valproate
  - Comatose

- Referred to neurology

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Update

CRP 326

Diagnosis: Sepsis Associated Encephalopathy

Sepsis Associated Encephalopathy

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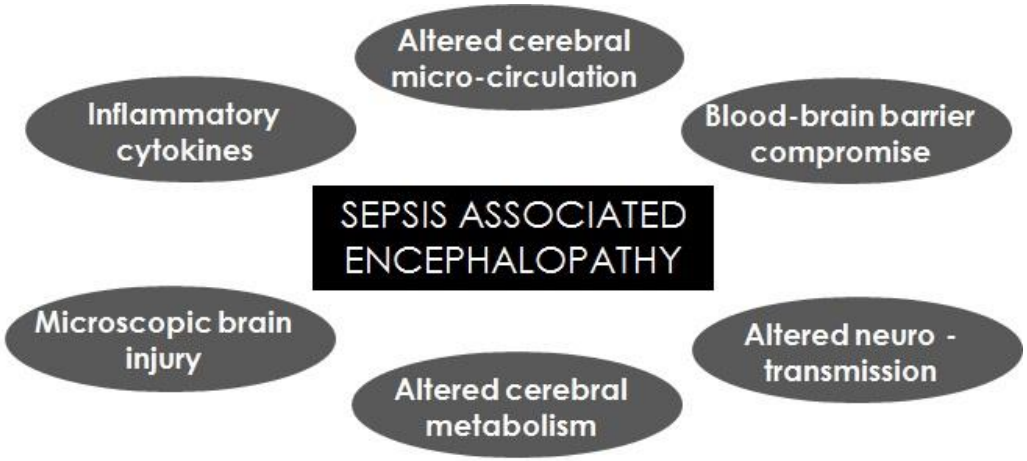
Acute Neurology
Update

- Brain dysfunction due to systemic sepsis, not primary CNS infection



- SAE may precede other manifestations of systemic sepsis
- Most common encephalopathy in medical / surgical ICU
  - 70% of all patients with bacteraemia (80% on EEG)
  - More common in multi-organ failure
- Increased mortality, cognitive impairment in survivors

Gofton TE, Young GB. Nat Rev Neurol. 2012; 8: 557-566.

True of false?

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Update

In a febrile encephalopathic patient, normal ESR and CRP decreases the likelihood of encephalitis

To what extent can clinical characteristics be used to distinguish encephalitis from encephalopathy of other causes? Results from a prospective observational study

Else Quist-Paulsen[1,2*], Anne-Marte Bakken Kran[2,3,4], Elisabeth S. Lindland[2,5,6], Katrine Ellefsen[7], Leiv Sandvik[8], Oona Dunlop[9] and Vidar Ormaasen[1]

BMC Infectious Diseases (2019) 19:80

NEANU
North of England Acute Neurology Update

- Acute medical admissions to large university teaching hospital
- 136 patients with encephalopathy
  - 19 met criteria for encephalitis
  - 117 had encephalopathy of another cause

- Clinical variables most strongly associated with encephalitis
  - Fever - OR 8.9 (1.7-46) p = 0.010
  - Nausea - OR 6.6 (1.6-28) p = 0.011
  - ESR <17 - OR 6.9 (1.5-32) p = 0.014

Elaboration of a clinical and paraclinical score to estimate the probability of herpes simplex virus encephalitis in patients with febrile, acute neurologic impairment

S. Gennai[1] · A. Rallo[1] · D. Keil[1] · A. Seigneurin[2] · R. Germi[3,4,5] · O. Epaulard[4,5,6]

Eur J Clin Microbiol Infect Dis (2016) 35:935–939

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North of England Acute Neurology Update

Neurologic history		Seizures		Systolic BP		CRP	
No	Yes	Yes	No	≥140 mm	<140 mm	<10 mg/L	≥10 mg/L
1	0	2	0	1	0	2	0

Total Score	Likelihood of HSV encephalitis
0	0.01 %
1	0.6 %
2	0.9 %
3	4 %
4	22 %
5	32 %
6	71 %

Case 3

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Acute Neurology
Update

PATIENT

VIDEO

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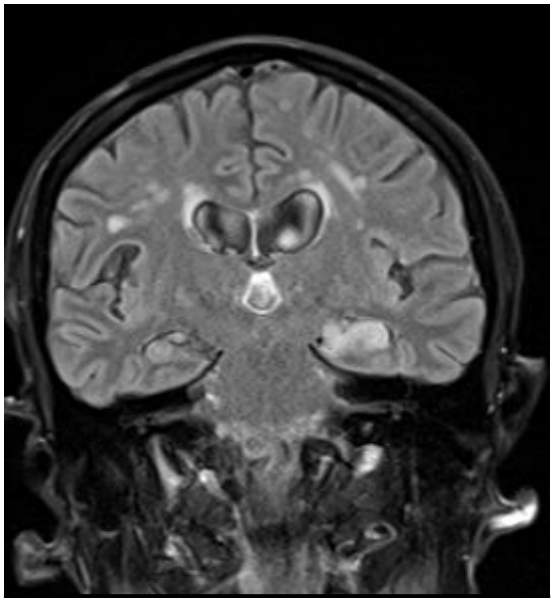

High T2 signal in the left hippocampus

This 62 year old man presented with encephalopathy. His serum sodium was 124. FBC, LFT, ESR, CRP normal. Hyponatremia was corrected, but encephalopathy persisted

Autoimmune limbic encephalitis with facio-brachial dystonic seizures due to antibodies to LGI1

Case 4

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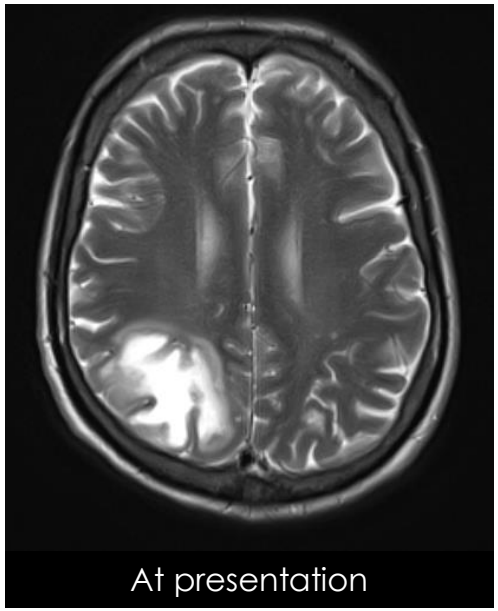
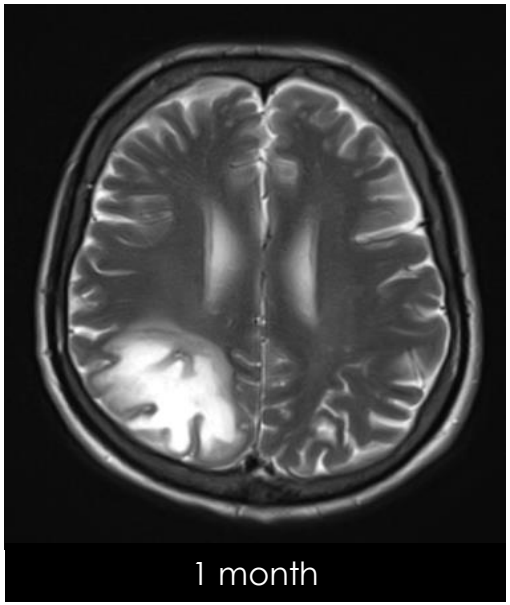
Acute Neurology
Update

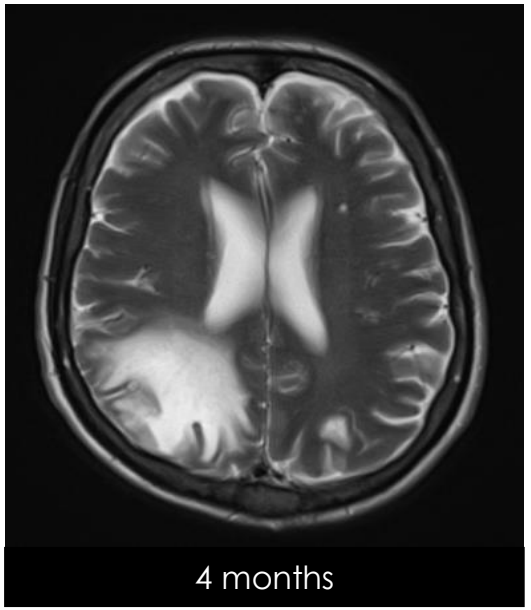
- 66 year old man
  - chronic lymphocytic leukaemia
  - chemotherapy with fludarabine
- Multiple episodes of seeing coloured balls of lights in the left visual hemi field
- One episode progressed to a generalised seizure
  - Following this patient remained confused
- MRI brain – white matter abnormality in the right occipital region



At presentation



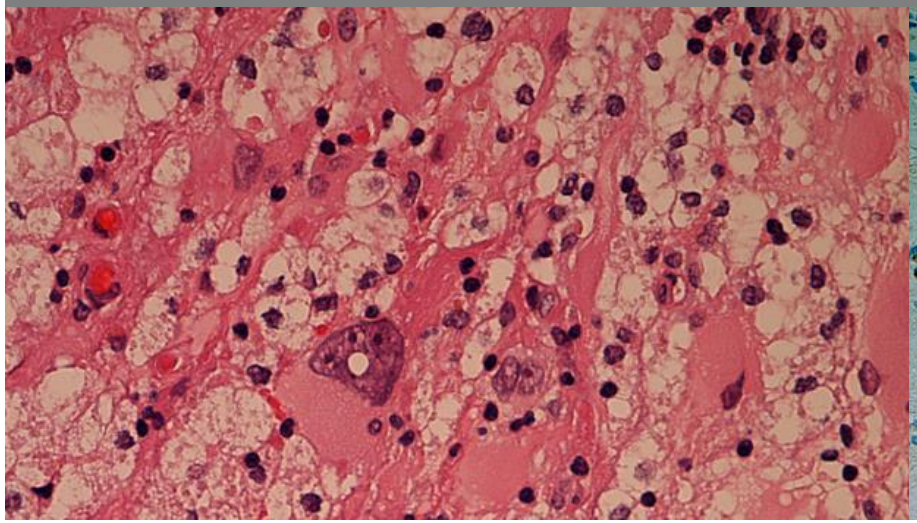
1 month

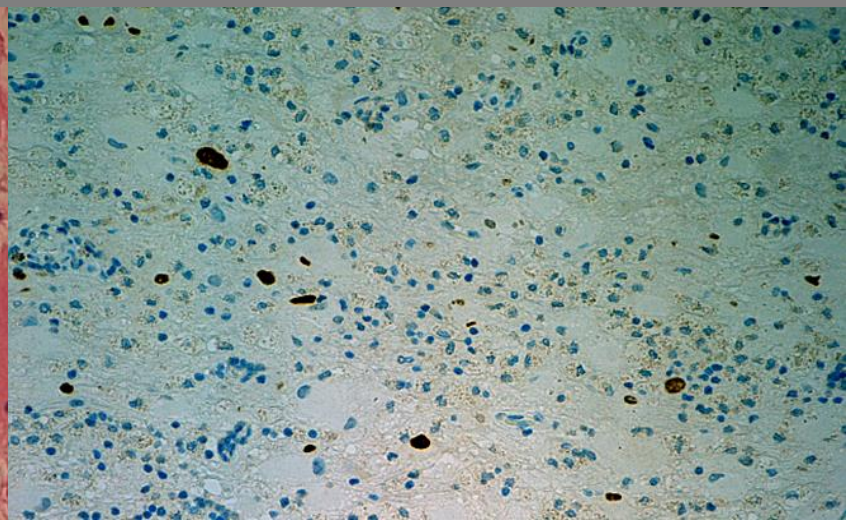


4 months

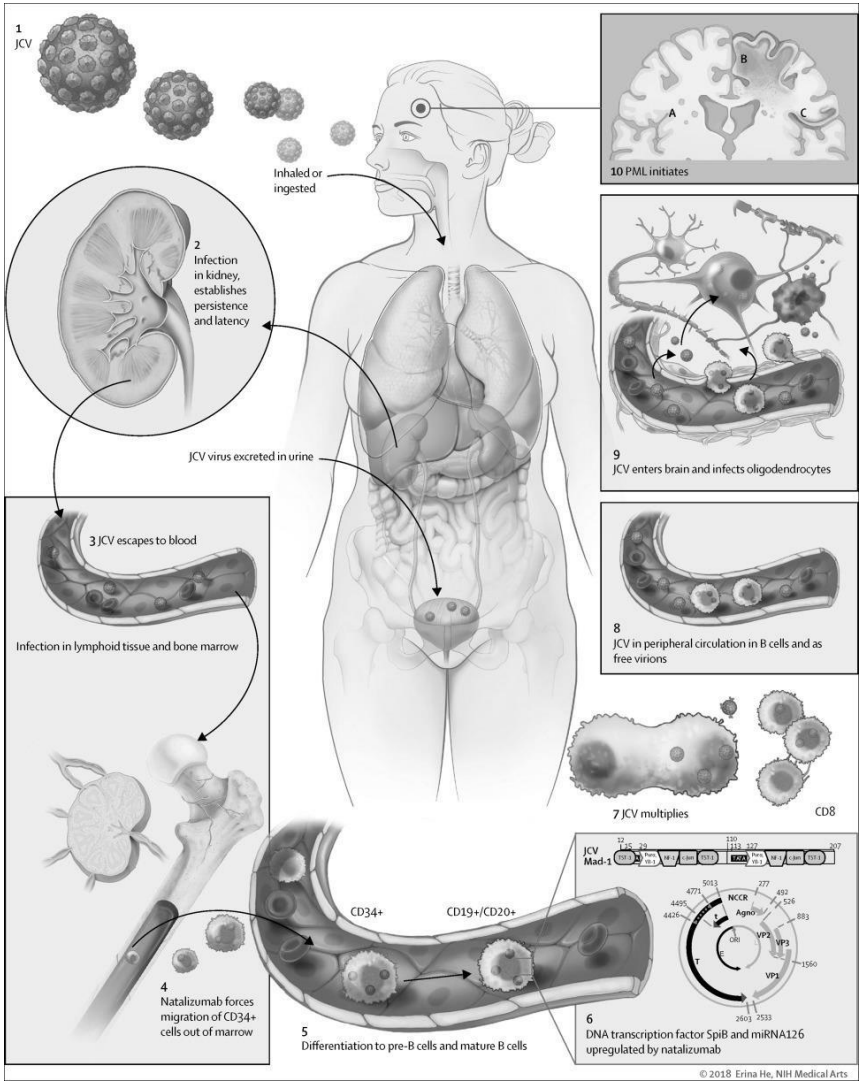
CSF PCR for JC and BK viruses negative

Brain biopsy: astrocytes with copious eosinophilic cytoplasm, irregular bizarrely shaped enlarged nuclei with nucleolar prominence. JC virus DNA detected by PCR, confirming the diagnosis of PML





PML



- Progressive multifocal leukoencephalopathy
- Caused by polyoma viruses JC and BK
- Infects oligodendrocytes in immunocompromised host
  - Cancer
  - HIV
  - Immunotherapy
- Causes progressive areas of demyelination
- Prognosis poor

Lancet Neurol. 2018; 17: 467-480

Case 5

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Acute Neurology
Update

- 52 year old man
- Seizures involving right leg
  - Controlled on lamotrigine
- MRI scan – primary brain tumour left hemisphere
  - Biopsy – oligodendroglioma
  - Treated with radiotherapy
- Tumour / epilepsy well controlled

- 7 years later
- Worsening gait, falls
- Admitted to DGH
  - UTI
  - Slow in responses
  - Short-stepped shuffling gait
  - No tremor
  - No rigidity / bradykinesia
  - ? Parkinson's disease

Serial scans

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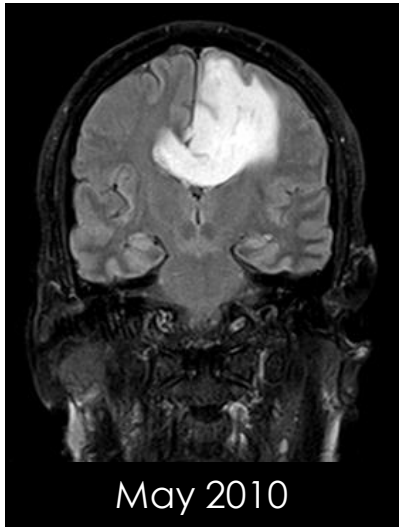
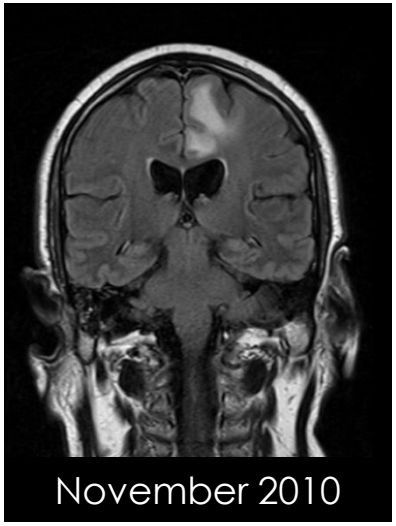
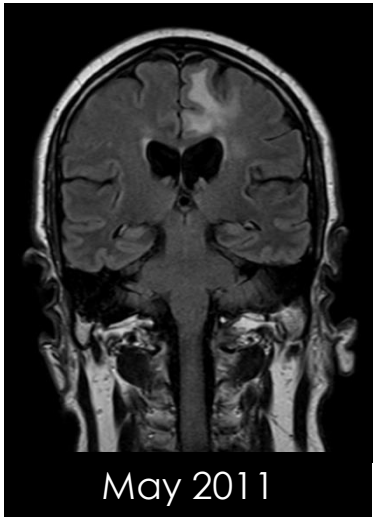
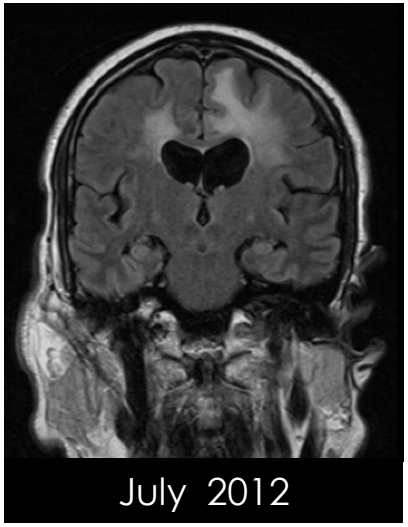
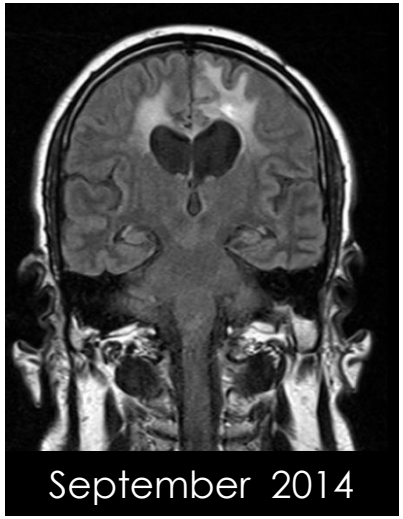
Update

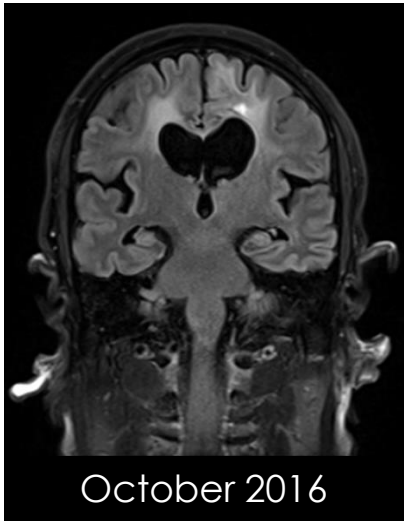

May 2010

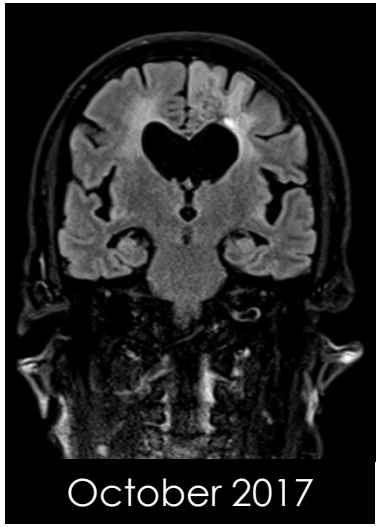

November 2010

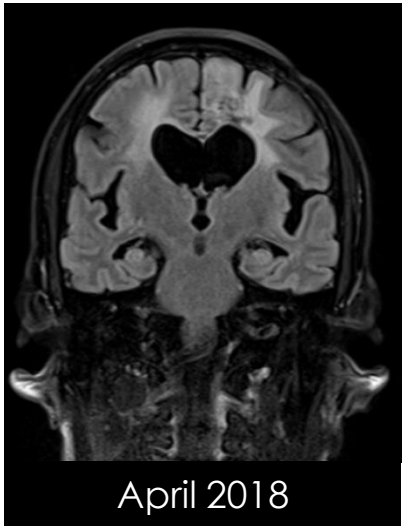

May 2011


July 2012

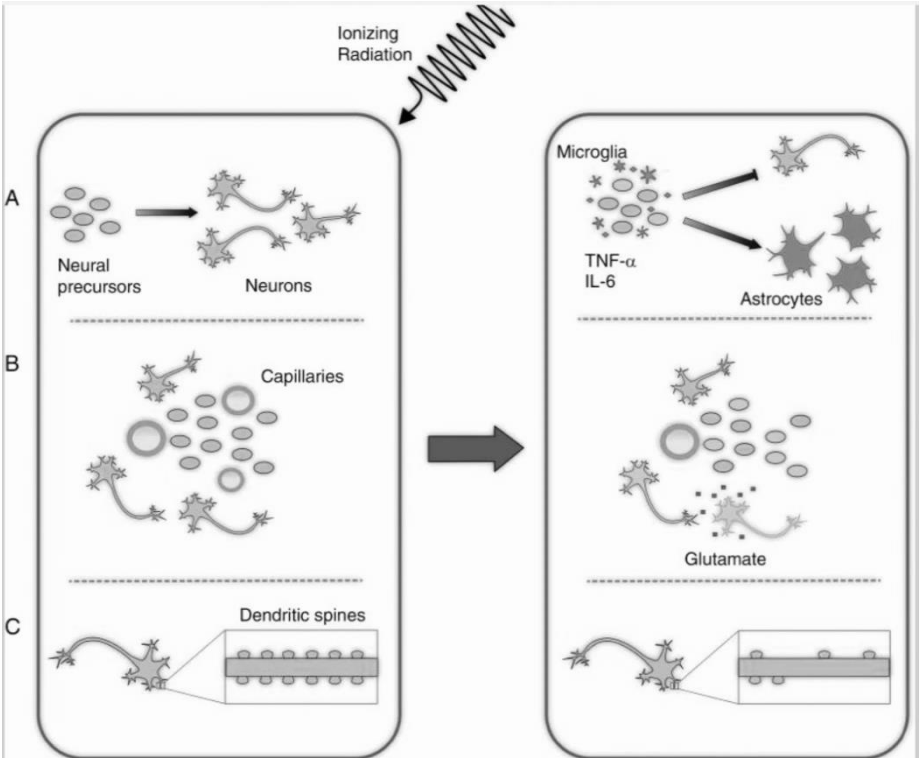

September 2014


October 2016


October 2017


April 2018

Radiotherapy effects on brain



- Acute, early delayed and late delayed radiation toxicity
- Late delayed toxicity
  - Progressive white matter change and micro-vasculopathy
  - Gait disorder
  - Cognitive impairment
- Vascular disorders
  - SMART syndrome
  - Cavernoma formation, Moya moya

Wilke et al. Neuro Oncol. 2018; 20: 597–607

Case 6

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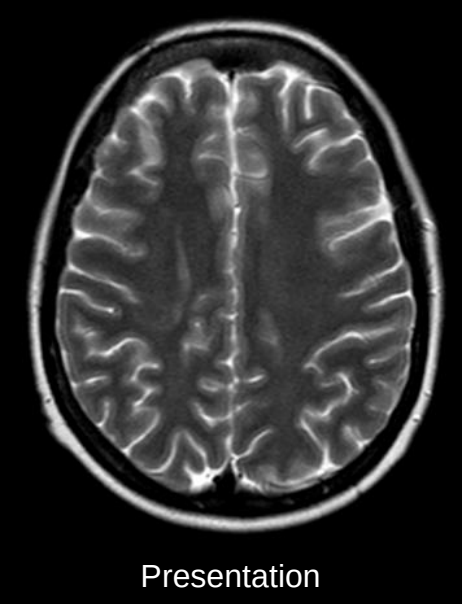
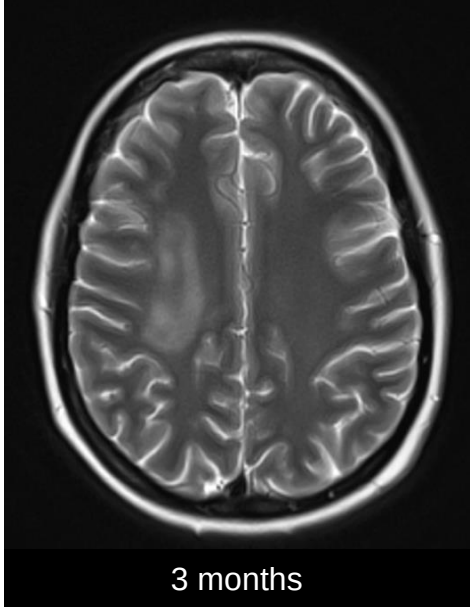
Update

- 36 year old lady
- Chondrosarcoma of the left knee
  - Above knee amputation
  - Chemotherapy with high dose methotrexate, cisplatin and doxorubicin
- Sudden onset of weakness of the left arm,
- MRI scan - T2 high signal in the right centrum semiovale
  - Diagnosed with TIA, started on aspirin
- The weakness resolved over a few days, but recurred 3 times in 4 weeks

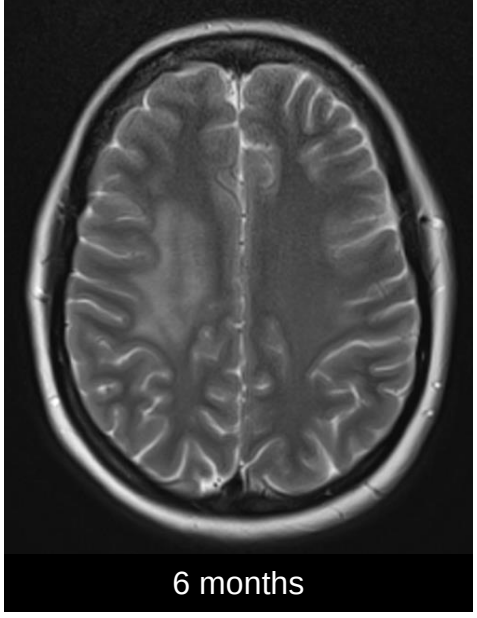
- Repeat MRI scan
  - Increasing white matter abnormality, ?PML
  - Methotrexate stopped
- CSF PCR negative for JC and BK viruses.
- metastatic cancer > died 15 months later.
- Post mortem
  - patchy low grade demyelination with myelin pallor and vacuolation, and axonal sparing. There were no areas of necrosis.
  - PCR was negative for JC and BK virus DNA.
  - Pathological changes characteristic of toxic leukoencephalopathy, likely related to metotrexate, exacerbated by co-medication with aspirin



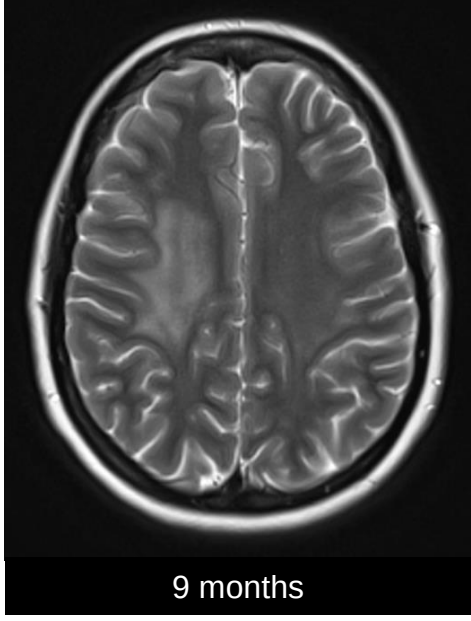
Presentation



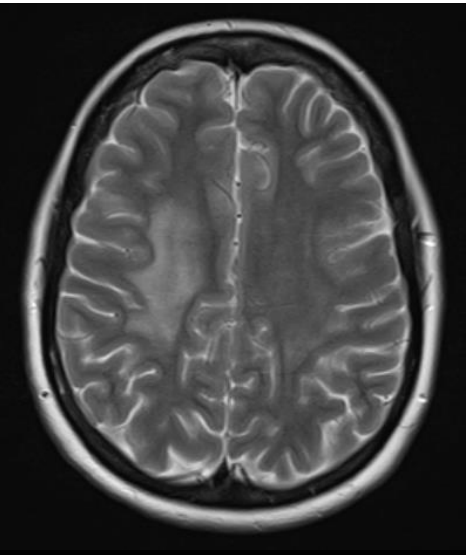
3 months



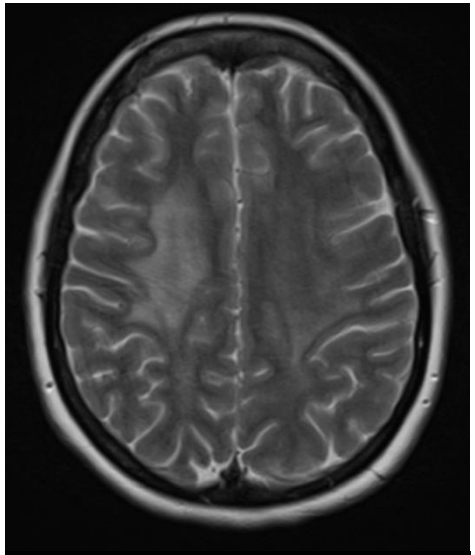
6 months



9 months

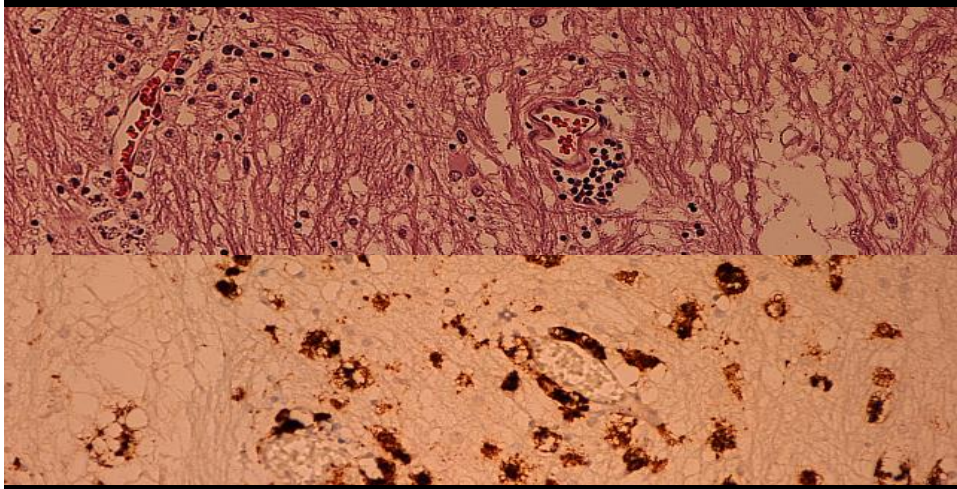


12 months



15 months

White matter vacuolations, scant perivascular lymphocytic infiltrates & limited number of reactive astrocytes (H&E x20)



Increased white matter macrophage infiltrates (CD68 x20)

Toxic leukoencephalopathy

NEANU
North of England
Acute Neurology
Update

- Demyelinating damage to white matter
  - toxins such as heroin, cocaine
  - chemotherapeutic and immunosuppressive agents
  - Eg: methotrexate, fludarabine, rituximab.
- 3 and 10% of patients receiving intrathecal methotrexate develop TLE
- dysfunction of the blood brain barrier (overlap with PRES)
- direct toxic effect on oligodendrocytes.
- Usually transient and reversible
  - If exposure to toxin continues, necrosis can occur within the white matter lesions

	PML	TLE	PRES
Clinical Picture	Several weeks to months. Stroke mimic. Motor & vision abnormalities, aphasia, seizures, personality change, cognitive decline[1].	Within 2-8 weeks[2,3]. Often transient. Stroke mimic. Confusion, dysarthria, hemiparesis, ataxia [4].	Hours to months[8]. Headache, reduced consciousness, seizures, paresis, visual disturbances, change in mental state[9,10,11].
Imaging	Posterior regions including brainstem, cerebellum and occipital lobes T1 hypointense T2 & FLAIR hyperintense Decreased ADC in new lesions[1].	Cytotoxic oedema in the corona radiata and centrum semiovale[3,5]. DWI hyperintense[5] FLAIR & T2 become hyperintense over time[6] Decreased ADC[3].	Vasogenic oedema in parietal and/or occipital lobes [11,12]. May involve grey matter[10]. T1 & DWI hypointense T2 & FLAIR hyperintense[11] Increased ADC[8]
Histology	'Bizarre' astrocytes irregular in shape with lobulated nuclei. Reactive astrocytosis and macrophage invasion. Oligodendrocytes with viral inclusion bodies[1].	Myelin pallor, oligodendroglial swelling, foamy macrophages and gliosis [3,7].	Demyelination, reactive astrocytosis, scattered lymphocyte & macrophage infiltration, vascular wall thickening[12]. Rarely fatal so limited evidence.