Rare Cases in Neurology:
HIV Neurology

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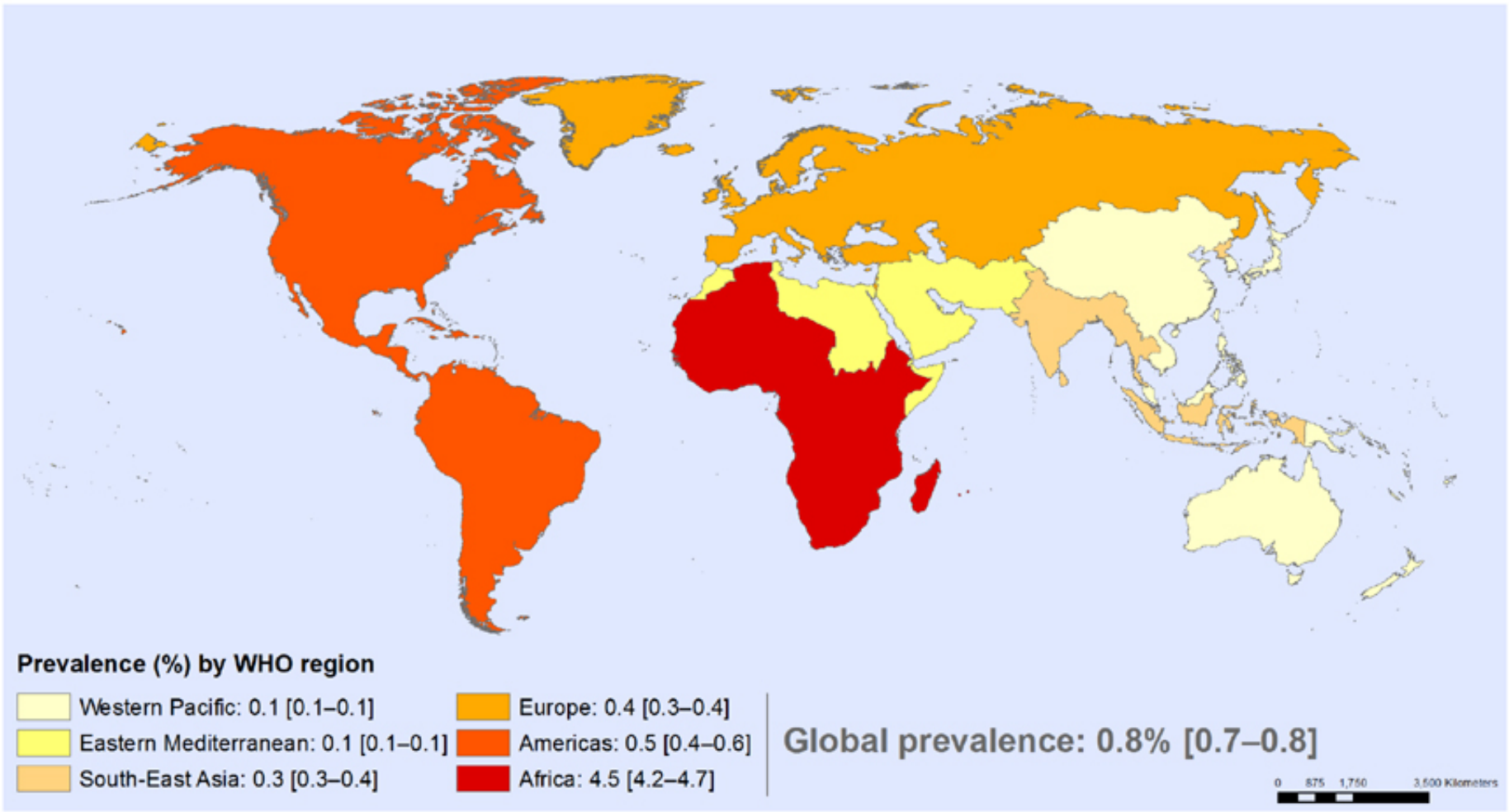
Introduction

- What is the *Human Immunodeficiency Virus*?
  - Retrovirus (ssRNA); possesses reverse transcriptase
  - Infects:
    - CD4 T helper cells
    - Macrophages
    - Dendritic cells
    - Microglia
  - *Lymphotropic & Neurotropic*
  - M-tropic (CCR5); T-tropic (CXCR4)
  - HIV-1 & HIV-2
  - HIV-1 clades (A to E) – B commonest US & Europe

Adult HIV prevalence (15–49 years), 2013
By WHO region

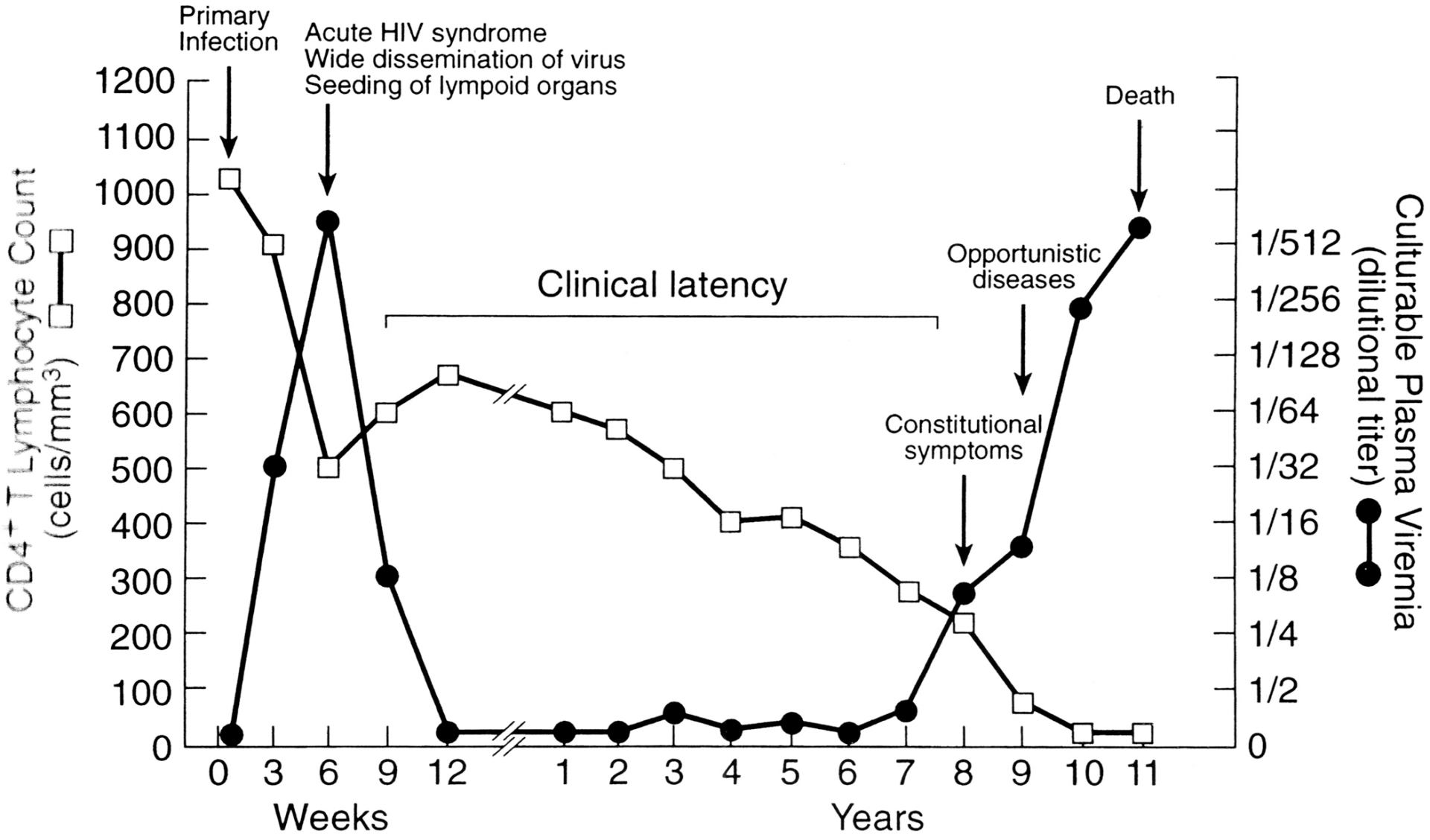


Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

World Health Organization

Global estimate of infected persons: 35 million

Natural History of Untreated HIV Infection



Principles of HIV Neurology

- **Time Locking**
  - Relationship to CD4 cell count
- **Parallel Tracking**
  - Involvement of multiple parts of the nervous system
- **Layering**
  - Different pathologies superimposed
- **Unmasking**
  - Second pathology dominated by subacute first pathologies symptoms e.g. HIVE & Cryptococcus

Brew (2001) HIV Neurology *OUP*

Neurological Complications of Immunosuppression

Box 7 Neurological complications of HIV

CD4 T cell count/μl	Opportunistic infection	Direct HIV related neurological complications
>500		► Aseptic meningitis/meningoencephalitis ► Guillain–Barré syndrome
200–500	► Tuberculous meningitis	► Chronic inflammatory demyelinating polyneuropathy ► Mononeuritis multiplex ► HIV driven distal symmetrical axonal sensory polyneuropathy ► Antiretroviral drug related toxic distal symmetrical axonal sensory polyneuropathy ► HIV headache
50–200	► Cryptococcal meningitis ► Cerebral toxoplasmosis ► Progressive multifocal leucoencephalopathy	► Vacuolar myelopathy ► Autonomic neuropathy ► HIV dementia ► Primary CNS lymphoma (Epstein–Barr virus related)
<50	► CMV polyradiculopathy/mononeuritis multiplex/encephalitis	

All complications listed at higher CD4 cell counts can occur at lower CD4 cell counts. Progressive multifocal leucoencephalopathy can occur at higher CD4 cell counts.

Davies, N. & Thwaites, G. Infections of the nervous system. *Pract Neurol 11, 121-131 (2011).*

Case 1

- 30s RH MSM Caucasian
- HIV-1 diagnosed 6 years before presentation
  - Symptomatic seroconversion
  - No OIs; no cART (fully sensitive virus)
  - No past medical history of note

Case 1

- Initial symptoms
  - Tingling numbness in distal LLs
  - Little pain
  - Ascended over 6-week period
- Subsequently similar symptoms in tips of fingers
- No Lhermitte's or Uthoff's phenomena
- No sphincter disturbance

Case 1

- Prior to first neurological review difficulties standing on heels & tiptoes
  - Loosing balance
  - Fine finger movements not affected
- Neurological referral to local unit
  - Smokes 20 cigs/day; occ alcohol; no illicit drugs; broad diet; dietary supplements
  - O/E No weakness; hyporeflexic; normal vibration sensation & light touch
  - Routine neuropathy screen unremarkable

Nerve Conduction Studies - 1

MNCV Data			Lat *ms*	Amp *mv*	Dur *ms*	Dist *mm*	CV *m/s*
R	Tibial						
	Ankle	- AH	5.0	2.4	7.9		
	Pop Fos	- Ankle	16.8	2.4	6.0	420	35.6
R	Tibial						
	H-Refl	- Soleus	Absent				
L	Tibial						
	Ankle	- AH	5.3	1.7	8.1		
	Pop Fos	- Ankle	15.4	1.0	12.5	420	41.6
	F Min	- AH	58.2				
L	Tibial						
	H-Refl	- Soleus	Absent				
R	Ulnar						
	Wrist	- ADM	3.7	4.1	8.4		
	B Elbow	- Wrist	9.7	4.1	10.0	310	51.7
	F Min	- ADM	31.9				
L	Ulnar						
	Wrist	- ADM	4.6	2.2	7.2		
	B Elbow	- Wrist	10.3	2.2	7.8	300	52.6
	F Min	- ADM	31.5				

Nerve Conduction Studies - 1

SNCV Data			Lat *ms*	Dur *ms*	Amp *μV*	Dist *mm*	CV *m/s*
R	Median						
	F2	- Wrist	Absent				
L	Median						
	F2	- Wrist	Absent				
R	Radial						
	Forearm	- Hand	2.2	2.3	6	120	54.5
L	Radial						
	Forearm	- Hand	Absent				
R	Sural						
	Ankle	- Calf	Absent				
L	Sural						
	Ankle	- Calf	Absent				

Comment

Nerve conduction studies of the upper and lower limbs show abnormalities suggesting a severe distal, axonal, large fiber sensorimotor peripheral neuropathy.

Case Presentation

- Referred to HIV Neurology Clinic
  - Seen 2/12 later; substantially better neurologically
  - O/E EHL 4- /4+
    - Absent ankle jerks
    - Vibration sensation normal
    - One error of proprioception Rt great toe
    - Hyperpathia to PP to ankles
    - Cranial nerves & UL examination unremarkable

HIV Biomarkers

Date	CD4 count (cells/uL)	Viral Load (copies/mL)
May 2010	428	25,000
November 2010	547	30,000
April 2011	534	130,000
June 2011	287	111,000

Baseline Investigations

- FBC; renal, liver, bone & thyroid profiles; CRP
- ESR 9 mm/hr
- Random plasma glucose 5.6 mmol/L
- B12; red cell folate; IgG, IgA, IgM; protein electrophoresis
- ANA; ANCA; ganglioside antibodies
- Hepatitis B & C; syphilis serologies
- Triglycerides
- Chest radiograph

Case Presentation

What did we do?

Case Presentation

What did we do?

- Initiated cART
  - Atripla (Tenofovir; Emtricitabine; Efavirenz)
  - After 4 weeks CD4 469 cells/uL; VL 180 copies/mL

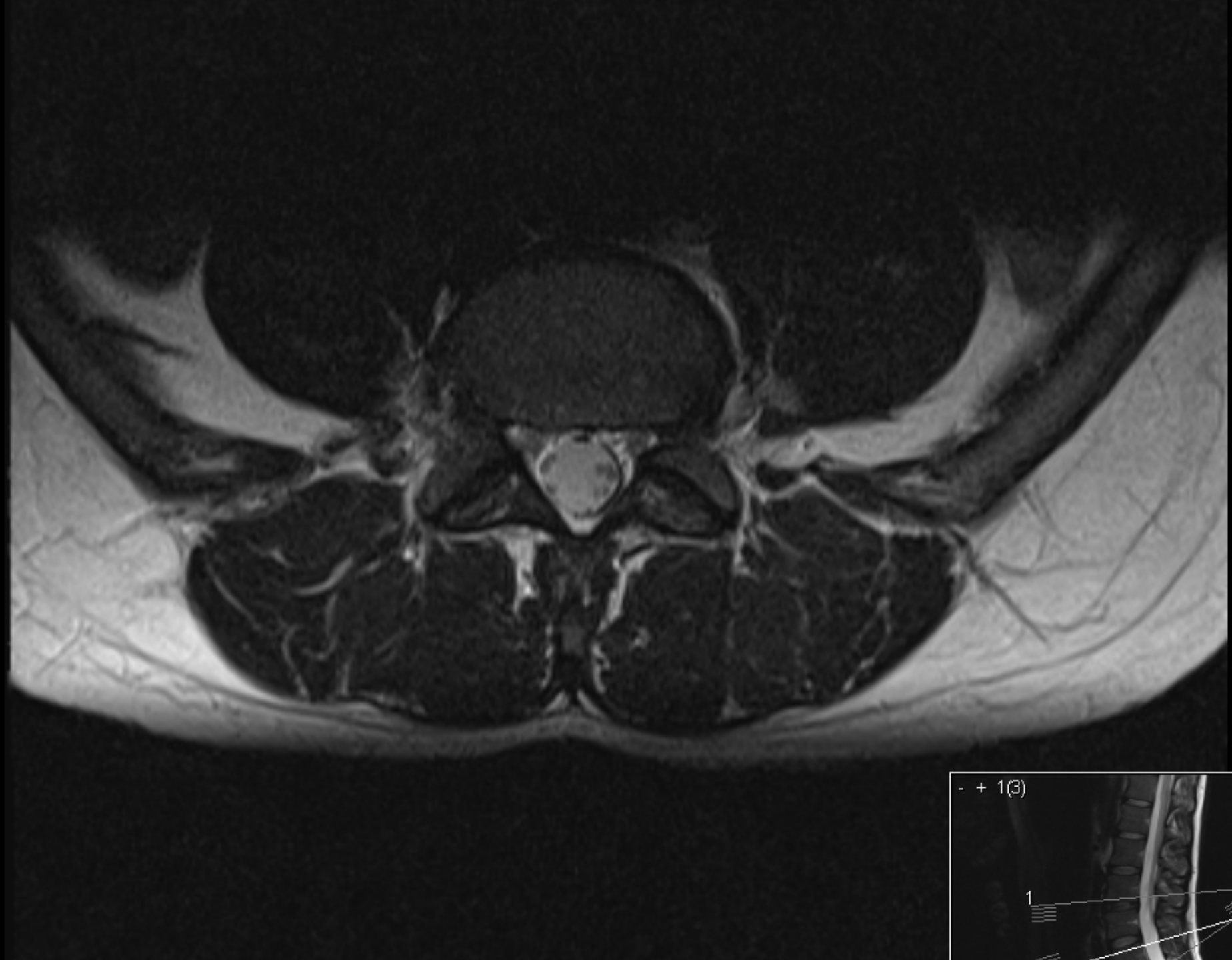
Case Presentation

- 5 weeks following initiation of cART recurrence of symptoms
  - Sensory & motor
  - O/E Symmetrical LL weakness of knee flexion & extension (4+); ADF/APF (4); EHL 4-
    - UL normal power
    - Areflexic U & LL
    - Impaired Vib to knees; PP hyperpathia to knees; JPS to ankles; Romberg's +ve

Nerve Conduction Studies -2

- Absent sensory responses
- Moderately increased distal motor latencies
- CMAP dispersion
- MCV slowing (<30m/s in LL;)
- F-wave dispersion

Features of demyelinating neuropathy with motor conduction block.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Cerebrospinal Fluid Examination

- CSF
  - WCC <1 / uL RCC <1/uL
  - Protein 2.5 g/L
  - Glucose 4.5/6.0
  - CRAG –ve; culture negative; HSV, VZV, CMV, EBV, JCV & enterovirus PCR negative

- Treated with single 5-day course of ivIg (0.4g/kg/day)

Case Presentation

- HIV-related Chronic Inflammatory Demyelinating Polyradiculopathy (CIDP)

- Asymptomatic & normal neurological examination

Why not HIV-DSPN?

- Involvement of upper limbs
- Lack of pain (but did have hyperpathia)
- Prominent motor involvement
- Early involvement of large fibres / abnormal NCS
- Spontaneous remission
- CD4 cell count >200 cells/uL

HIV Neuropathies

- HIV-DSPN
- Antiretroviral toxic neuropathy
- *Zoster (sine herpete) (radiculopathy)*
- Inflammatory demyelinating neuropathies
  - AIDP / CIDP
- Mononeuritis multiplex
  - Vasculitic (nb hep B or C co-infection)
  - CMV
- Diffuse Infiltrative Lymphocytosis Syndrome (DILS)
    - Painful DSPN; parotidomegaly & sicca syndrome with CD8 lymphocytic infiltration

Further Reading

- Robinson-Papp, J. & Simpson, D.M. Neuromuscular diseases associated with HIV-1 infection. *Muscle Nerve* ***40, 1043-1053 (2009).***

- The Neurology of AIDS 3rd Edition (2011) Gendelman et al; OUP

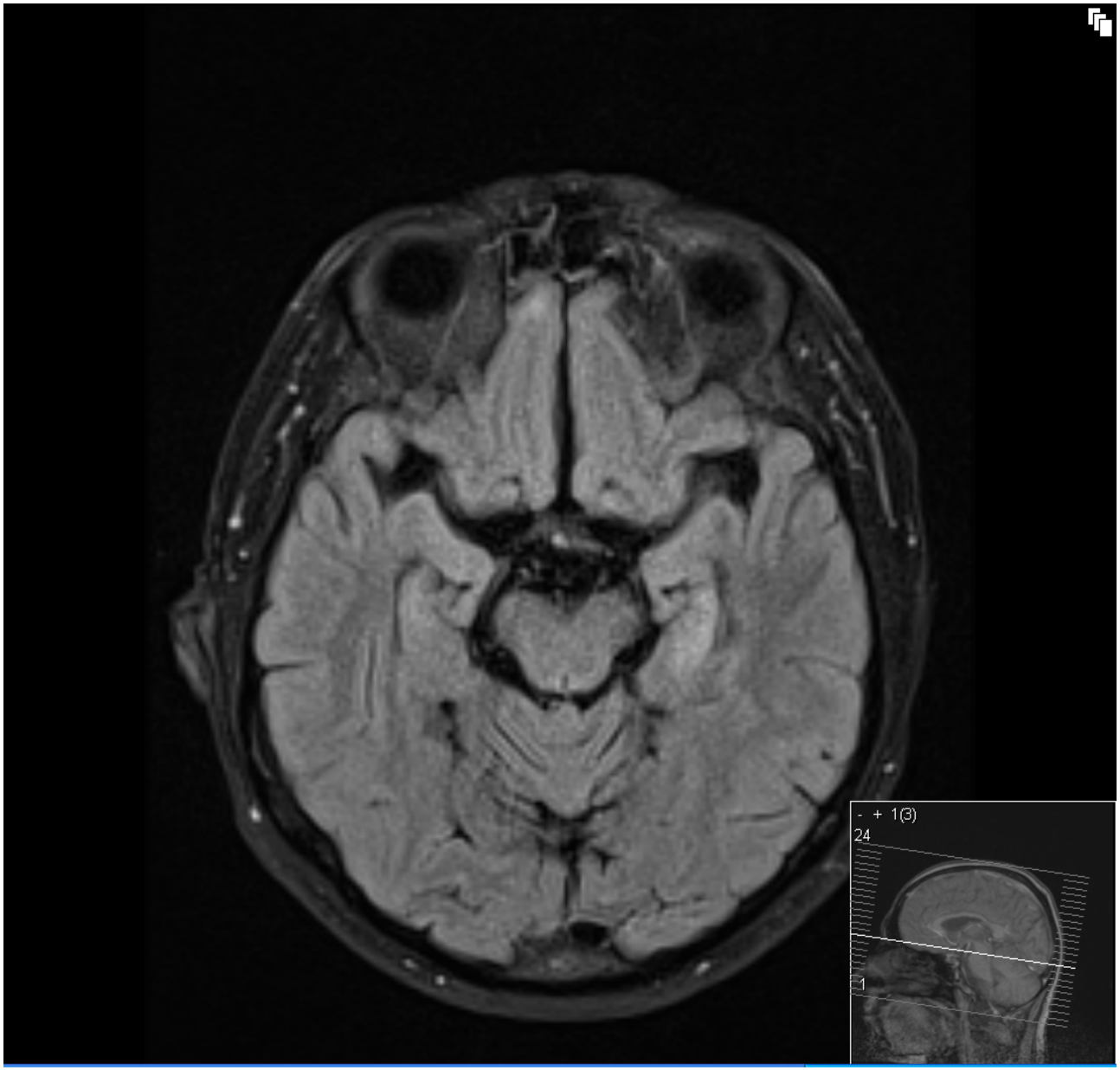
Case 2

- 54-yr-old, RH, woman
  - HIV-1 Infection
    - Diagnosed early 1991
    - KS 1994/2001 (Rt medial leg)
    - Nadir CD4 cell count – not known
    - cART started
      - AZT monotherapy 1994
      - 2008 to admission TFV; FTC; rATZ
      - Aug 2012 CD4 805 cells/uL VL <40 copies/mL

Neurological Presentation

- Admitted to local hospital with unprovoked recurrent seizures
  - 1/52 prior had toe amputation at (chronic osteomyelitis); discharged on oral flucloxacillin
  - Seizures managed with iv phenytoin
  - Ceftriaxone & aciclovir initiated
  - CTH—NAD; LP WCC 1 cells/uL; RCC 5 cells/uL
  - Transferred to C&W
    - Alert & orientated
    - Afebrile
    - No focal neurology

Imaging: Axial FLAIR Nov 2012



Management

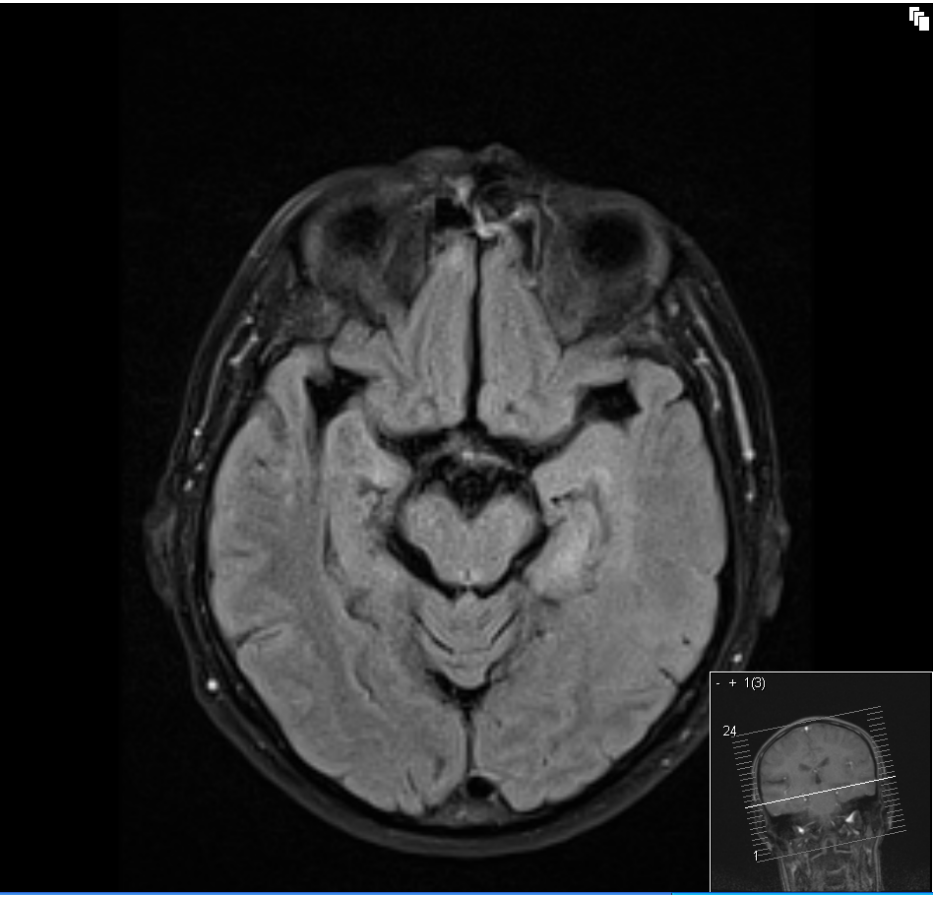
- Other tests
  - Routine bloods
  - Serologies: syphilis; *Toxo*; ANA; ANCA; ACA; Lupus
  - Anti-neuronal; GAD; VGKCC; NMDA
  - EEG - normal
  - ?Limbic encephalitis
    - Home on Keppra

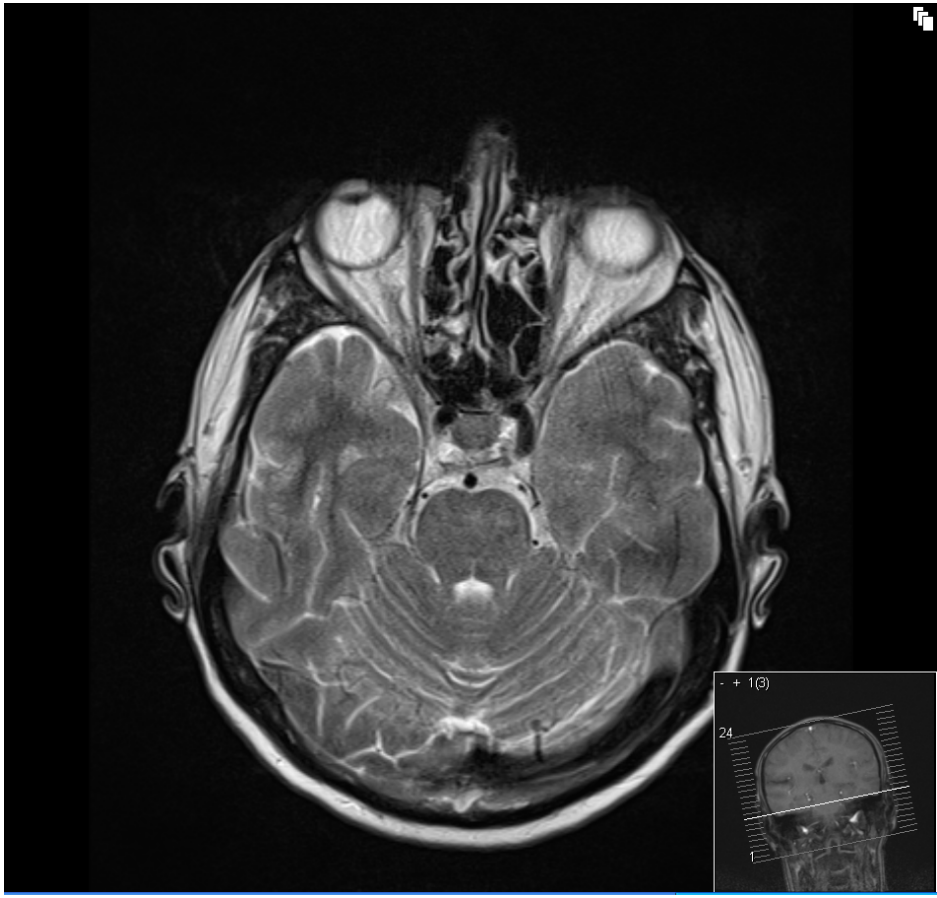
Neurological Developments

- Re-admitted Dec 2012
  - Nausea & vomiting
  - Unsteadiness of 3/7 duration
    - No further seizures
    - “Nystagmus”
    - Gait ataxia; milder finger-nose dysmetria
    - Minimal myoclonus

Video

Axial FLAIR & T2





CSF & other parameters

- CSF
  - WCC 32 cells/uL (50% polys); RCC 2 cells/uL
  - Prot 0.86 g/L OCB C+S-
  - Gluc 3/5.8 mmol/L
  - PCR –ve HSV; VZV; CMV; EBV; JCV; EV; *Toxo*; 16s RNA
  - CRAG –ve
  - AFB; routine culture –ve
- CT whole body PET
- CT chest, abdo, pelvis
- Anti-neuronal antibodies; autoimmune screen; tumour markers

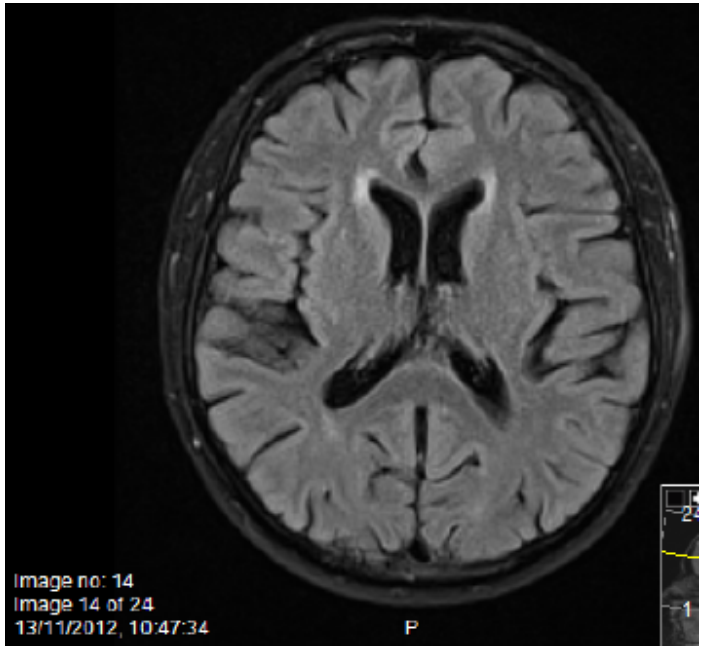
Management

- Listeria cover for 3/52
- ivlg
- Clonazepam
- CSF VL from Dec 2012 630 copies/mL
  - NRTI resistance K65R; M184V
  - NNRTI none
  - PI major resistance mutations: M46IM

Previous ARV combinations

2008- 2012:	TFV; FTC; rATZ
2002-2007:	3TC; TFV; ABC; LPV
2000-2002:	TFV; dDI; LPV; ABC
2000-2000:	d4T; dDI; rIND
1999-2000:	d4T; dDI; EFV
1996-1999:	3TC; AZT
1994:	AZT

- New regimen: AZT; 3TC; Tenofovir; ritonavir-boosted Darunavir; Raltegravir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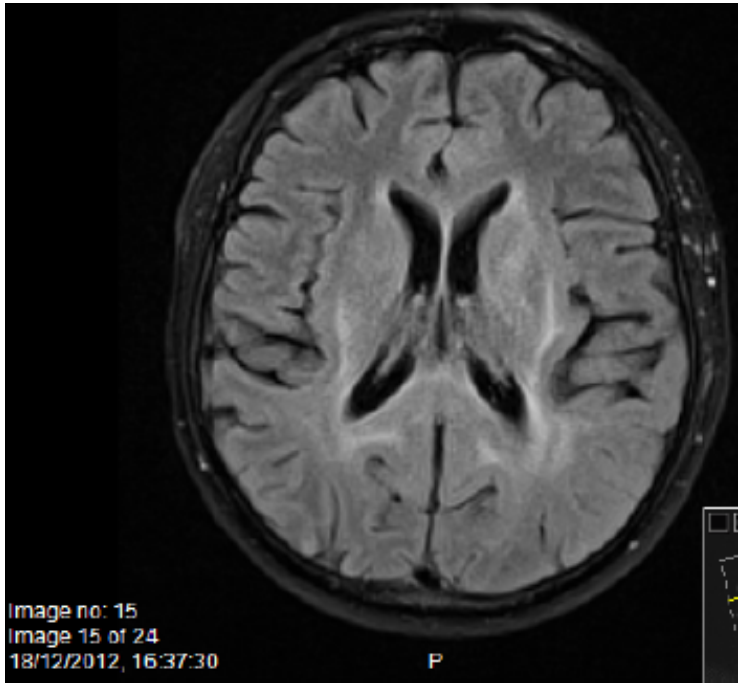
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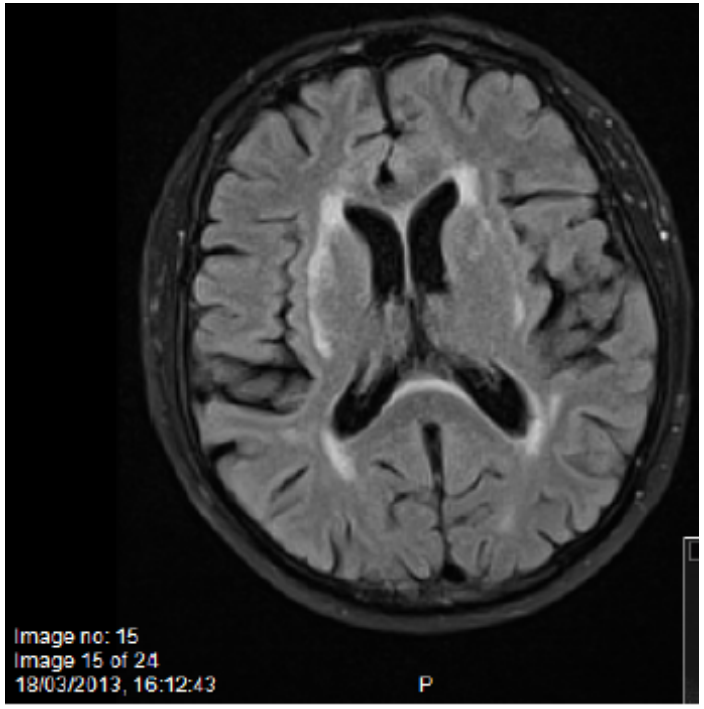
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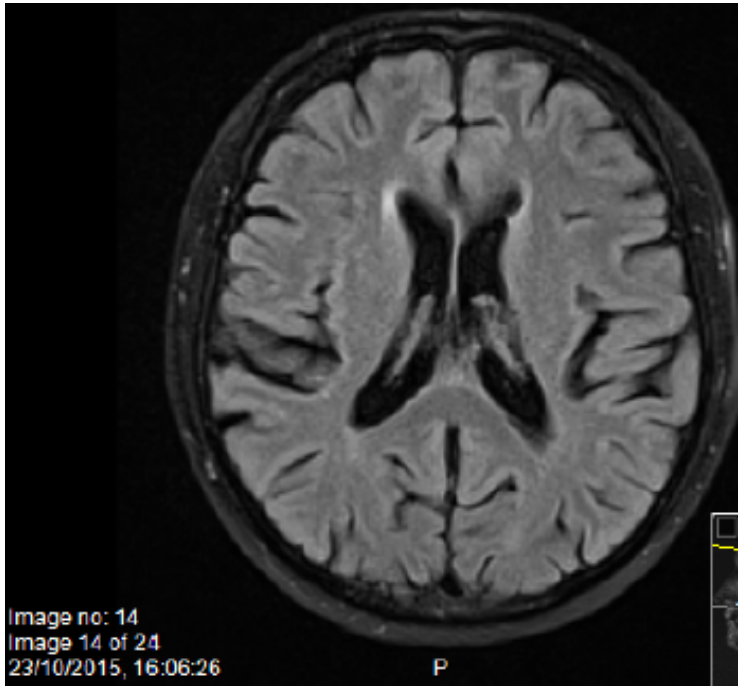
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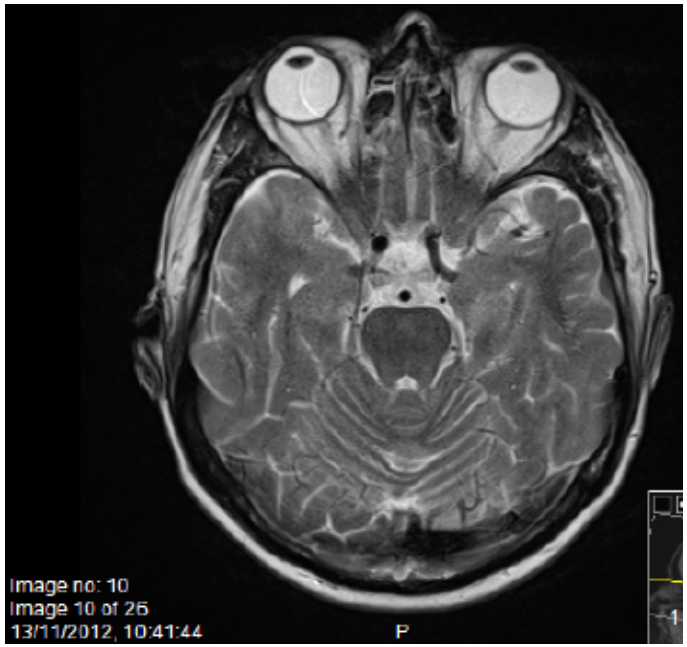
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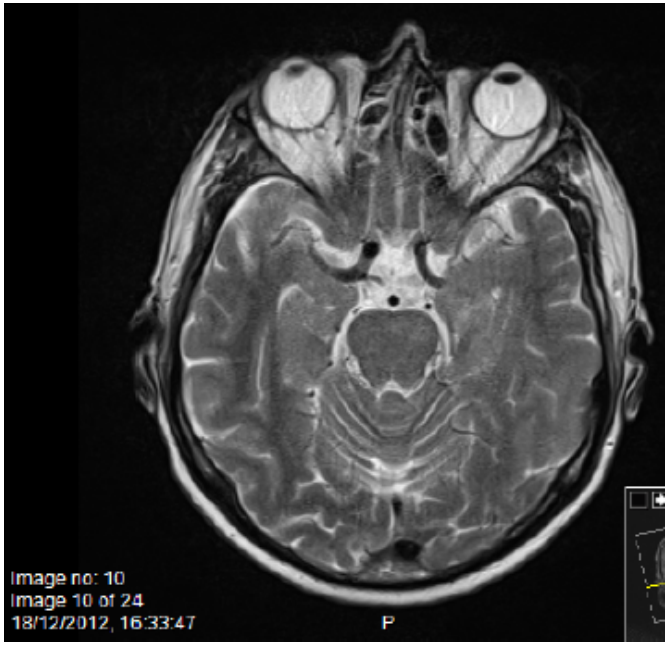
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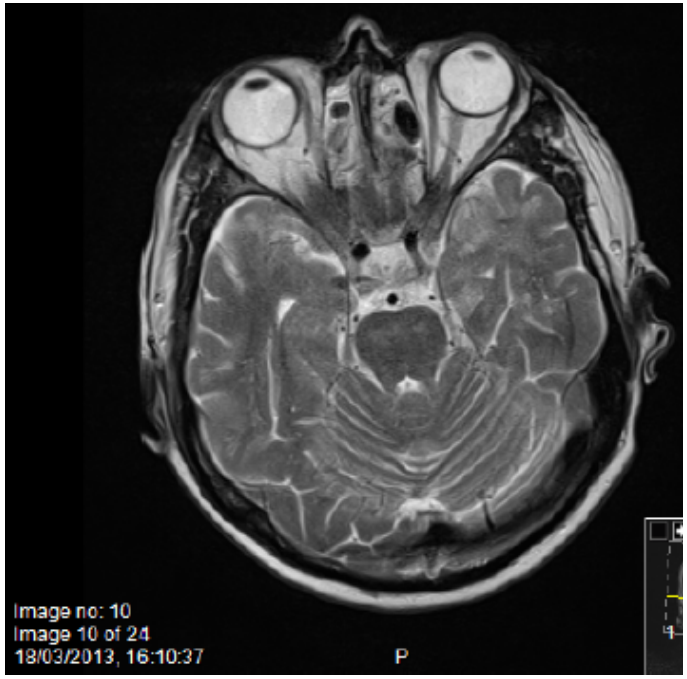
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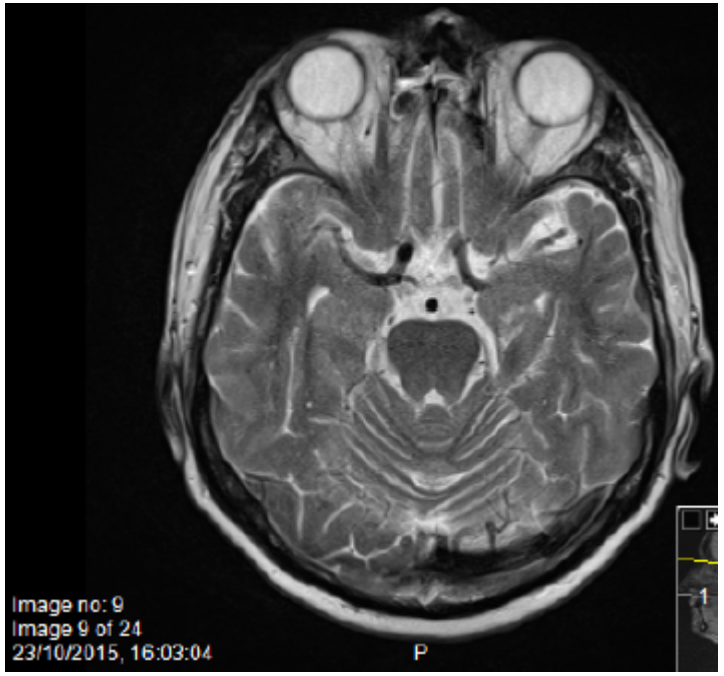
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CSF Sept 2013

- WCC <1 cell/ul; RCC <1 cell/uL;
- Prot 0.42 g/L
- S100b 0.15 ng/L (tau/AB also normal)
- CSF HIV VL – undetectable

- Seizure-free; normal gait; recreational dancing

Literature

Literature: cases relate to HIV or IRIS

1: Wiersinga WJ, Prins JM, van de Beek D. Therapy-resistant opsoclonus-myoclonus syndrome secondary to HIV-1 infection. Clin Infect Dis. 2012 Feb 1;54(3):447-8.

2: Kanjanasut N, Phanthumchinda K, Bhidayasiri R. HIV-related opsoclonus-myoclonus-ataxia syndrome: report on two cases. Clin Neurol Neurosurg. 2010 Sep;112(7):572-4. doi: 10.1016/j.clineuro.2010.03.024

3: Scott KM, Parker F, Heckmann JM. Opsoclonus-myoclonus syndrome and HIV-infection. J Neurol Sci. 2009 Sep 15;284(1-2):192-5.

4: Ayarza A, Parisi V, Altclas J, Visconti D, Persi G, Rugilo CA, Gatto EM. Opsoclonus-myoclonus-ataxia syndrome and HIV seroconversion. J Neurol. 2009 Jun;256(6):1024-5

5: van Toorn R, Rabie H, Warwick JM. Opsoclonus-myoclonus in an HIV-infected child on antiretroviral therapy--possible immune reconstitution inflammatory syndrome. Eur J Paediatr Neurol. 2005;9(6):423-6.

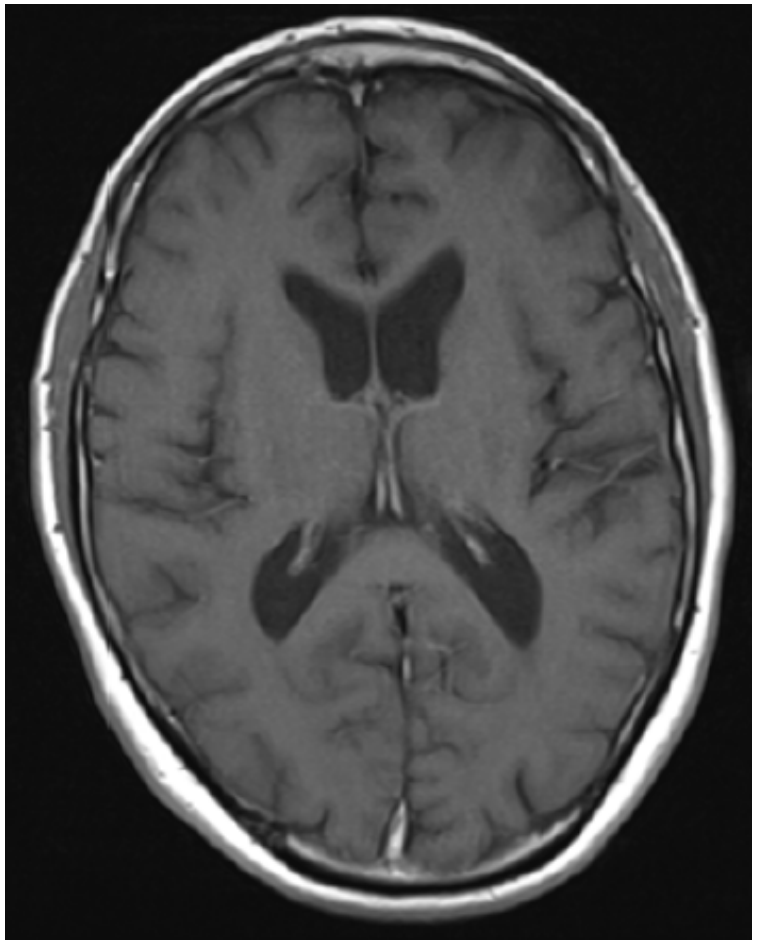
Case 3

- 44-yr-old RH Caucasian
- HIV-1 recently diagnosed following presentation with PJP (CD4 nadir 62 c/uL; VL $9x10^6$/mL)
  - 6/52 ago started cART (Truvada & ritonavir-boosted Darunavir)
  - Type-1 DM
  - Develops “confusion”

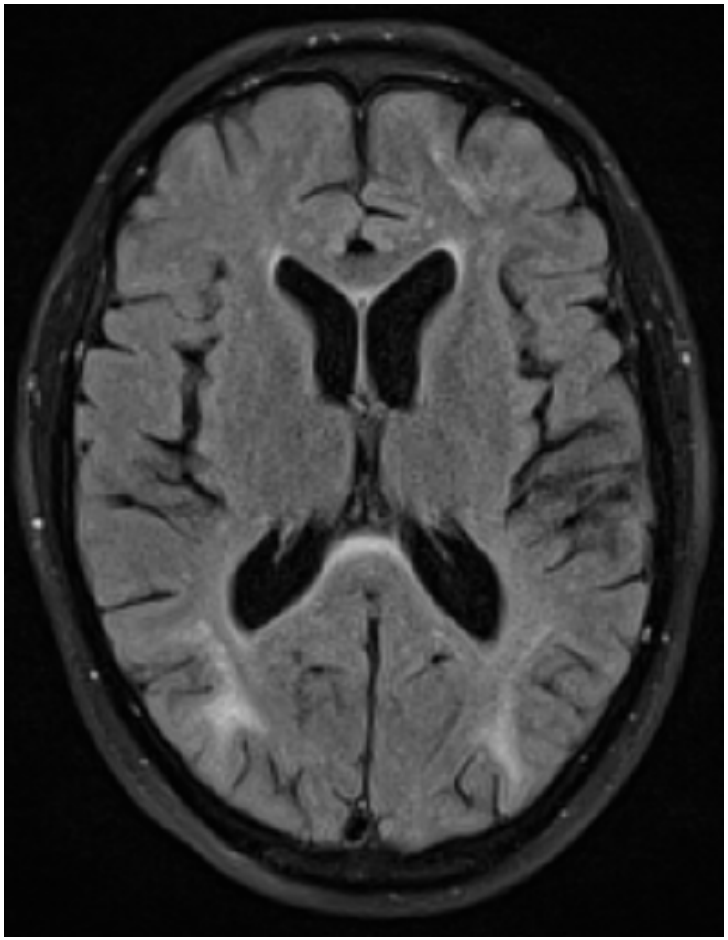
Case 3

- Subacute onset cognitive decline: difficulty reading, recurrent falls.
- By admission:
  - Disorientated in time & place
  - Rt>Lt skew deviation, full range of movement; broken pursuits; flat discs. Normal pupillary responses.
  - Lt homonymous heminanopia
  - Rt pronator drift; clumsy finger movements; symmetrical brisk DTRs; flexor plantars
  - Impaired attention & recall; concrete thinking; poor cognitive estimates; profoundly apraxic (RT>LT)
  - ACE (III): 45/100 [Attention 9/18; memory 15/26; fluency 1/14; language 18/26; visuospatial 2/16]

14/8/15



Axial T1 with contrast



Axial FLAIR

Case 3

- Investigations:
  - CSF: WCC <1 c/uL; prot0.62 g/L; glucose 5.9/21.3 mmol/L
  - CD4 88 c/uL (8.6%); VL 204 c/mL
  - Routine blood tests unremarkable save for glucose, HBA1c 53 mm/mol, & GAD antibodies (13u/L)
  - TT echo
  - ANA; ANCA; ACA; Lupus anticoagulant; VGKCC; NMDAR; neuronal antibodies negative.
  - Hepatitis A & B immune; hepatitis C & syphilis seronegative
  - Chest radiograph – normal
  - CT intracranial angiogram – normal

Case 3

- Investigations:
  - CSF PCR results:
    - HSV; VZV; CMV & enterovirus nucleic acid –ve
    - EBV DNA +ve (2000 copies/mL)
    - JCV DNA positive
  - CSF Cryptococcal antigen –ve; routine culture & mycobacterial culture negative
- Treatment:
    - ARVs: Raltegravir; Truvada; Maraviroc
    - Mirtazepine (30mg); Fluconazole; Cotrimoxazole

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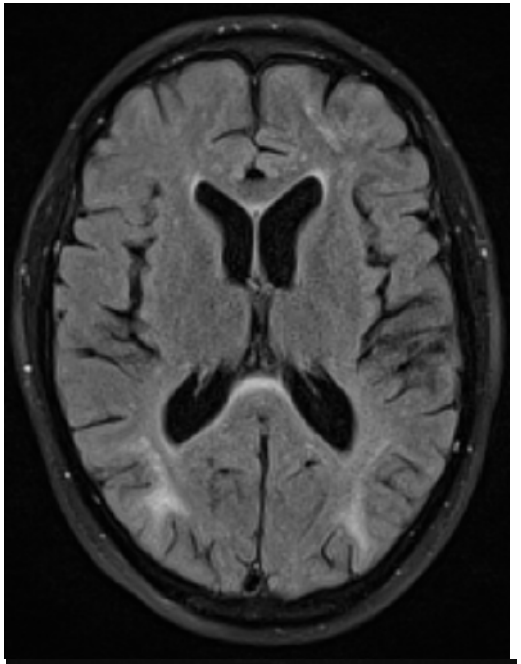

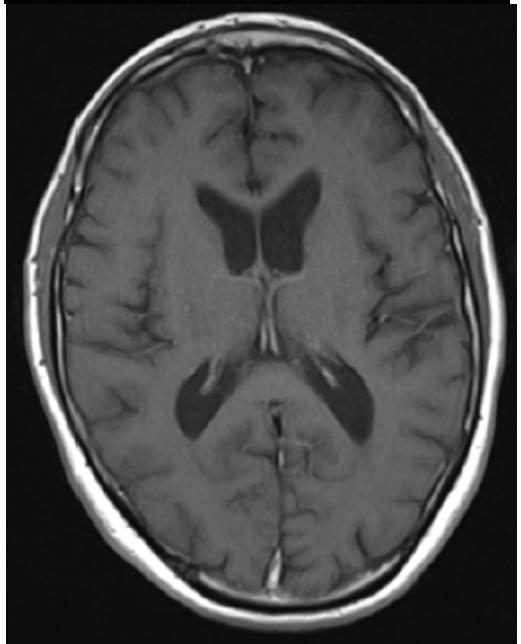

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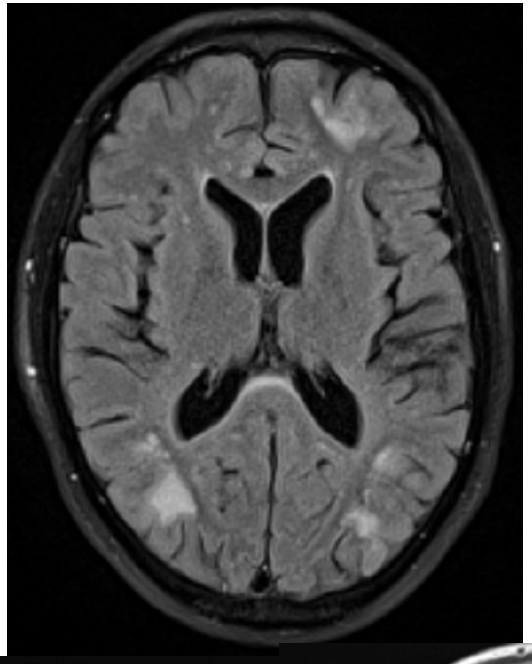

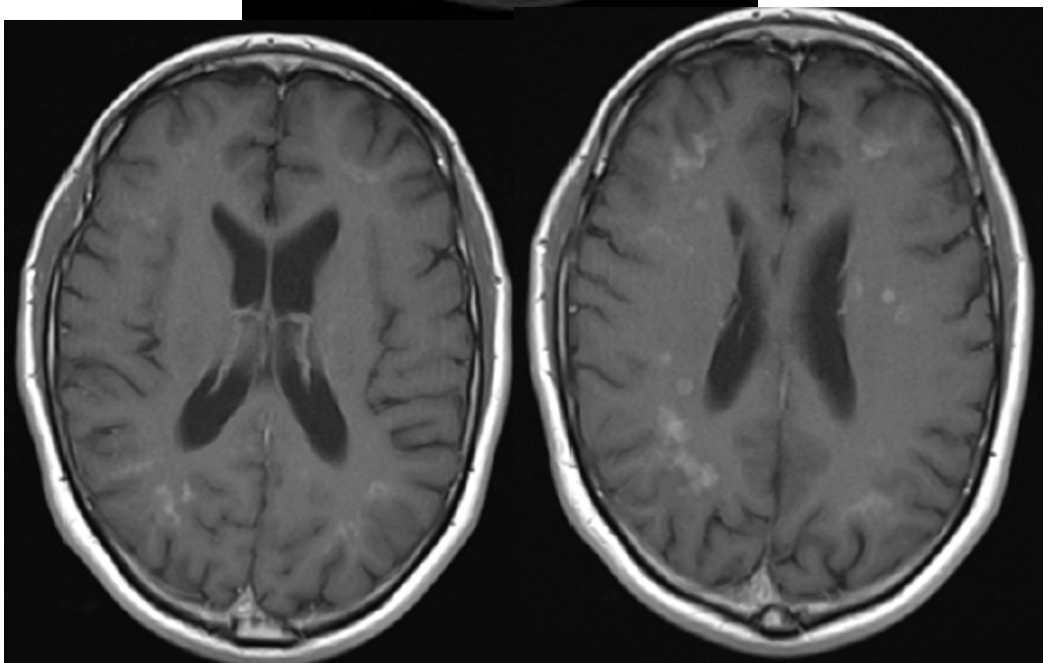

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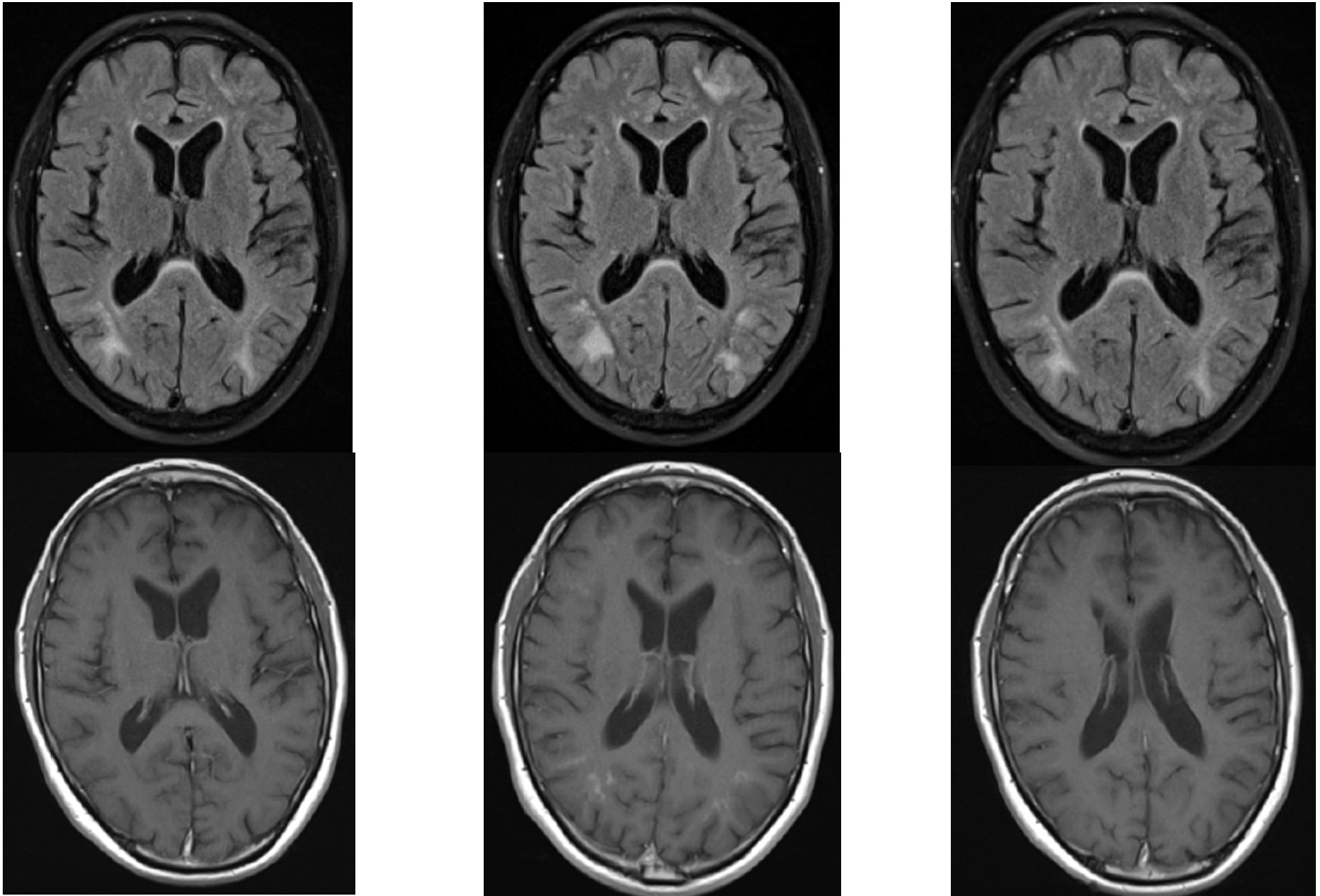


Immune Reconstitution Inflammatory Syndrome (IRIS)

- Definition:

"a paradoxical deterioration in clinical status attributable to the recovery of the immune system during HAART."

- Other examples in neurological practice
  - Reversal reactions in leprosy
  - MS relapse following pregnancy
  - Cessation of natalizumab in MS
  - Tuberculoma development in treated-TBM
  - Stroke in *S pneumoniae* meningitis

Johnson, T. & Nath, A. Neurological complications of immune reconstitution in HIV-infected populations. *Ann N Y Acad Sci 1184, 106-120 (2010).*

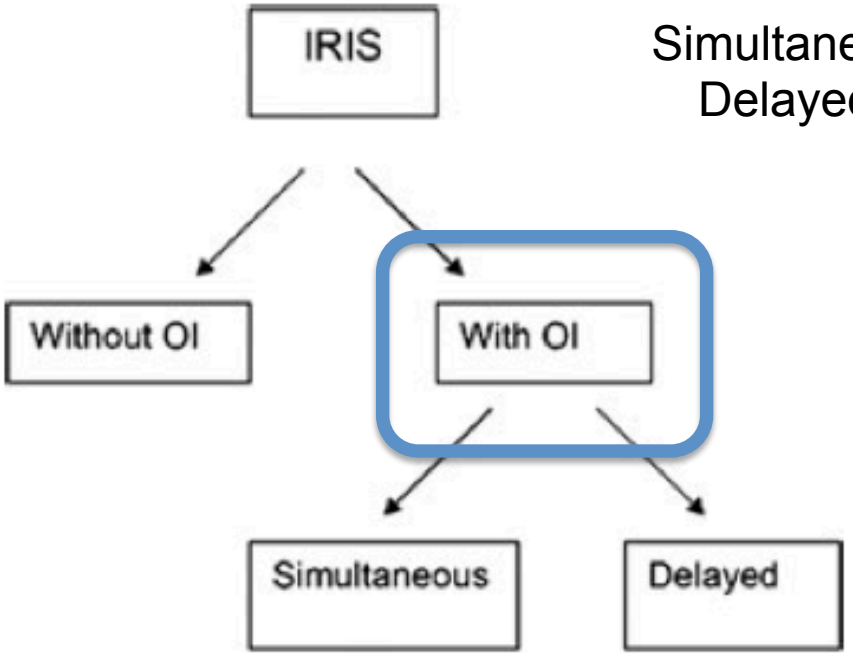
IRIS: Epidemiology

- Incidence varies between cohorts
  - 10-45% including all organs
    - Resource-rich setting: CNS-IRIS – 0.9%[1]
    - Resource-poor setting: CNS-IRIS – 28%[2]
  - Incidence relates to associated OI
- Mortality
  - Significant
    - Crypto-IRIS 20%
    - MTB-IRIS (CNS) 13%

[1] McCombe, J.A., Auer, R.N., Maingat, F.G., *et al. Neurologic immune reconstitution inflammatory syndrome in HIV/AIDS: outcome and epidemiology. Neurology 72, 835-841 (2009).*

[2] Asselman, V., Thienemann, F., Pepper, D.J., *et al. Central nervous system disorders after starting antiretroviral therapy in South Africa. AIDS 24, 2871-2876 (2010).*

IRIS: Classification[1]



Simultaneous = Unmasked
Delayed = Paradoxical

Figure 1. Types of IRIS: IRIS following initiation of HAART may occur in the presence or absence of an opportunistic infection (OI). In some, the OI may first become clinically apparent concurrently with the IRIS and hence termed "simultaneous IRIS." In others, the OI predates the initiation of HAART but subsequently results in IRIS. This has been termed "delayed IRIS."

Johnson, T. & Nath, A. Neurological complications of immune reconstitution in HIV-infected populations. *Ann N Y Acad Sci 1184, 106-120 (2010).*

IRIS Associated with CNS Opportunistic Infections

Microbe	Frequency	Neuro-IRIS	Extraneural-IRIS
JCV	17% (2-50)	Inflammatory PML	None known
MTB	16% (10-25)	Meningitis; tuberculoma; radiculomyelitis	Lymphadenitis; pulmonary infiltrates; pleural effusions; cutaneous abscess
Cryptococcus neoformans	20% (7-45)	Meningitis; cryptococcoma	Lymphadenitis; cavitating pneumonia; skin

Adapted from: Martin-Blondel, G., Delobel, P., Blancher, A., *et al. Pathogenesis of the immune reconstitution inflammatory syndrome affecting the central nervous system in patients infected with HIV. Brain 134, 928-946 (2011).*

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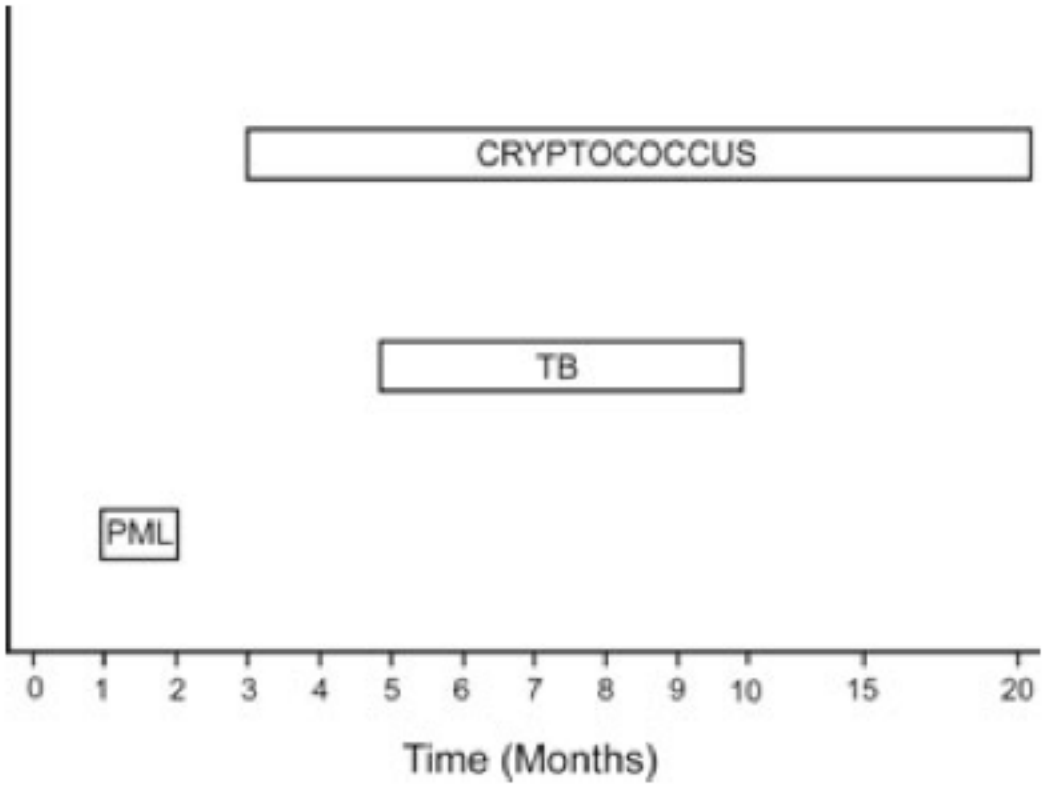
Microbe	Frequency	Neuro-IRIS	Extraneural-IRIS
JCV	17% (2-50)	Inflammatory PML	None known
MTB	16% (10-25)	Meningitis; tuberculoma; radiculomyelitis	Lymphadenitis; pulmonary infiltrates; pleural effusions; cutaneous abscess
Cryptococcus neoformans	20% (7-45)	Meningitis; cryptococcoma	Lymphadenitis; cavitating pneumonia; skin
MAC	Rare	Tuberculoma	Lymphadenitis; pulmonary infiltrates; pleural effusions; cutaneous abscess
Toxoplasma	Rare	Encephalitis	Retinitis
HSV	Rare	Encephalitis; myelitis	Genital ulceration
VZV	Rare	Vasculitis; myelitis	Dermatomal zoster
CMV	Rare	Encephalitis	Uveitis; retinitis; colitis
Parvovirus B19	Rare	Encephalitis; ventriculitis; brain vasculitis	Pure red cell anaemia
Syphilis	Rare	Encephalitis	Uveitis; ?skin

Adapted from: Martin-Blondel, G., Delobel, P., Blancher, A., *et al. Pathogenesis of the immune reconstitution inflammatory syndrome affecting the central nervous system in patients infected with HIV. Brain 134, 928-946 (2011).*

IRIS: Clinical



First manifestation of IRIS recorded from days until years after HAART initiation

Johnson, T. & Nath, A. Neurological complications of immune reconstitution in HIV-infected populations. *Ann N Y Acad Sci 1184, 106-120 (2010).*

Case 4

- 39-year-old. Male. Right-handed

- Attends HIV clinic for follow up
  - Generally feeling unwell
  - 2/52 viral gastroenteritis; seen in local hospital
  - Apyrexial
  - Systemic examination unremarkable.
  - RR 17, sats 100%, Temp 36.4, BP 161/90, HR 80bpm, BG 6.9mmol/l
  - Routine blood tests
- Na 111 mmol/L – admitted for investigations and management

Case 4

- Generally feeling unwell, and tired for last few weeks
- 5 week history of vivid dreams
  - "His friend giving birth to triplets"
  - "His other friends child dying"
- Sometimes wakes up distressed, agitated and anxious
- Hallucinations
  - Speaking to his father who does not live in London
- Constipated – not opened bowels for 4 days
- Lack of sensation when opening his bowels
- No headache and no photophobia
- Difficulty walking and feels generally weak

- Travelled to Turkey 1 month ago
- Took GHB/mephedrone 3-4/52 prior 2014

Case 4

Past medical history
- HIV diagnosed 3/12 prior to admission

Medications:
- Atripla started 6/52 prior to admission

Social history:
- Works full time promoting tourism
- History of illicit drug use has used GHB/ mephedrone over the last few years
- Alcohol 20 units / week.

Case 4: Examination

- Apyrexial
- Sweaty and clammy

- HR 130 bpm regular; BP 140/80. Normal heart sounds

- Respiratory and abdominal examination unremarkable.

- Cranial nerve examination – unremarkable. Tremulous
- Tone normal
- Power 5/5 throughout
- Normal sensation to light touch
- PR – normal anal tone

FBC – normal
CRP 2mg/L

Na 128 mmol/L K 3.9 Cr 76 Ur 8.9

Bil 11
ALT 220 u/L (0-40)
ALP 76. GGT 106 (<55)
Albumin 30 g/L
Corrected ca 2.13 mmol/L

CK 93 u/L

Urine Na 25
Plasma Osm 271 & Urine Osm 608 mOsm/L

Thyroid function normal
Cortisol 669 nmol/L

.

Hepatitis B surface antigen – negative
Hepatitis C antibody – negative
Hepatitis A IgG – positive. IgM negative

Syphilis serology negative

LDH 210
B12 and folate normal

Normal protein electrophoresis

ANA and ANCA negative

HIV viral load <40 copies/mL
CD4 – 513 cells/uL

Serum Cryptococcal antigen negative

Case 4

- CXR - normal
- CT Chest, Abdomen & Pelvis – normal
- MRI Brain – normal
- MRI Spine – normal

Case 4

- Vivid dreams and hallucinations. Which he attributes to the ARVs
- Appears distressed, agitated and very anxious

- Over the last week generally feels weak. More difficult to stand and walk
- Feel numb over his trunk
- Palpitations and sweaty.
- Slightly breathless.
- No headache and no photophobia

Examination

- Pyrexial 38 C HR 140 regular BP 150/90.
- MMSE 29/30 – dropping one point on orientation
- Bilateral LMN VII
- Neck flexion 4+/5 Neck extension 5/5
- Mild bilateral tremor. Present on action and posture
- Pin prick reduced over trunk and proximal part of limbs. Normal JPS
- Proximal weakness > distal
- Absent reflexes except triceps
- Coordination intact

	RUL	LUL		RLL	LLL
SAb	0	0	HF	1	1
EE	3	3	HE	3	3
EF	4	4	KF	4	3
WE	5	5	KE	4	4
WF	5	5	DF	5	5
FE	5	5	PF	5	5
FDIO	5	5			

	Right	Left
Bi	0	0
Br	0	0
T	(+)	+
K	0	0
A	0	0
P	Down	Down

Case 4

- CRP 102 mg/L
- Blood culture – *Klebsiella pneumonia*
- Na – 128 mmol/L. ALT 200 u/L

LP

- Opening pressure 18 cm H20
- WCC<1/uL; Protein 0.37 g/L; Glucose 4 mmol/L (blood 7.3)
- Cytology – acellular

Further information

- Originally from South Africa. Living in the UK for the last 16 years
- Had episodes of intermittent abdominal pain in the past with discoloured urine.
- Sometimes develops blisters in the sun

- Family history:
  - Maternal Grandmother – Porphyria

Case 4

Urinary porphobilinogen positive. Raised porphobilinogen and 5-aminolaevulininc acid (ALA)

Random urine

Total porphyrin	=	550	nmol/mmol creat	(Normal: <35)
Creatinine	=	18.8	mmol/L	
5-aminolaevulininc acid (ALA)	=	68.3	μmol/mmol creat	(Normal: <3.8)
Porphobilinogen (PBG)	=	38.2	μmol/mmol creat	(Normal: <1.5)

Atripla stopped

Klebsiella pneumonia treated with Tazocin

Started on a 4 day course of intravenous haeme-arginate 3mg/Kg

- 03/09/2014
- Deterioration in FVC <1 L
- Intubated

Random urine (04.09.14)

Total porphyrin	=	614	nmol/mmol creat	(Normal: <35)
Creatinine	=	11.4	mmol/L	
5-aminolaevulininc acid (ALA)	=	2.3	μmol/mmol creat	(Normal: <3.8)
Porphobilinogen (PBG)	=	0.5	μmol/mmol creat	(Normal: <1.5)

- 05/09/2014 given further four doses of haem arginate

- NCS/EMG
  - Sensory & motor nerve amplitudes reduced in U&LL
  - Conduction velocities normal (F-waves ULN)
  - EMG indicative of acute denervation. No myopathic features

Variegate Porphyria

- Autosomal dominant
- Deficiency of protoporphyrinogen oxidase
- Called variegate
  - Acute neurovisceral symptoms
  - Chronic blistering lesions on sun exposed areas of the skin
- Prevalance of VP is high in South Africans of Dutch descent
- Many remain asymptomatic. Low penetrance

Clinical features

- Abdominal pain. Extremity, back and chest pain
- Nausea, vomiting, constipation
- Bladder dysfunction and urinary retention are common
- Renal infarction and bowel intussusception
- Hyponatraemia – SIADH

- Peripheral neuropathy
  - Primarily motor. Proximal weakness. Axonal
  - Facial and bulbar weakness is common
  - Sensory impairment: glove and stocking or trunk and proximal limbs (bathing suit)
  - Pathogenesis unknown ?accumulation of ALA – leads to axonal damage or haem deficiency in the neuronal tissue

- Autonomic – tachycardia, hypo or hypertension etc.

- Agitation and psychotic features are common
- Seizures