Dead men do tell tales… Lessons learnt (the hard way)

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NIMHANS “Missing Links”

19th August 2016

MISSING LINK

- Illustrations…
- Lesson learnt….
- Do autopsies have a role in neuropsychiatric disorders?...

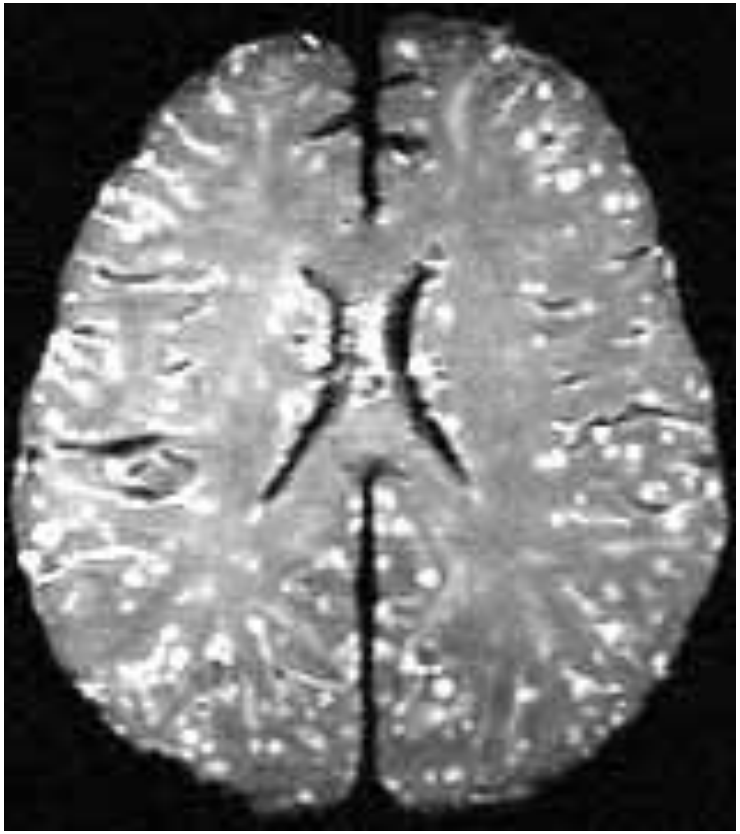
Case 1

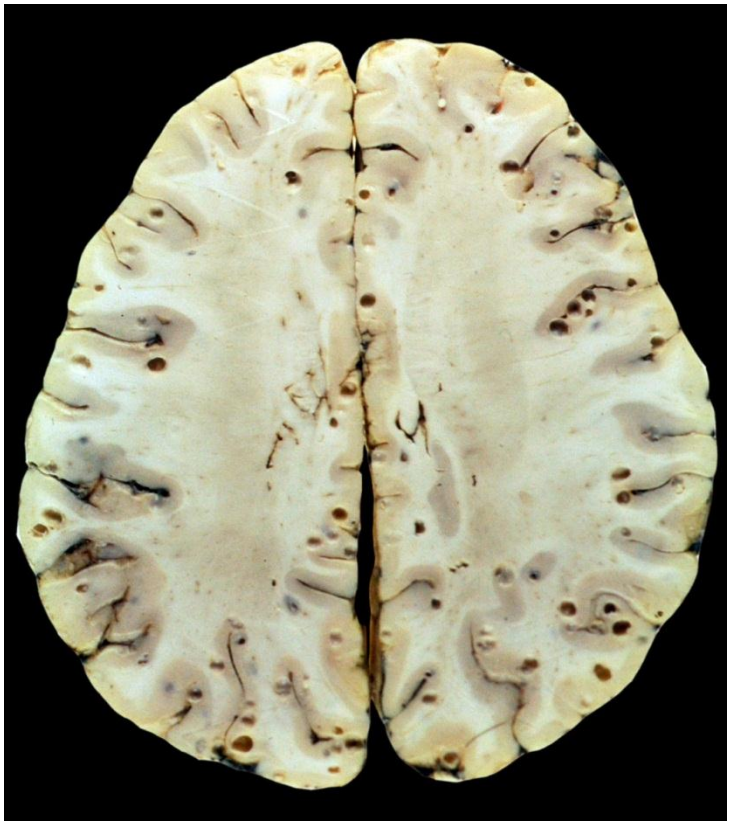
MISSING LINK

Case 1: Her-story

- 26 year old Hindu housewife, referred to Psychiatric services from a peripheral hospital for sudden onset abnormal behaviour.
- She had been admitted to local hospital for “alleged” burns inflicted following “dowry demands”. Her abnormal behaviour prompted referral to NIMHANS
- O/E she was dull, withdrawn, non communicative and not making eye to eye contact. CT scan was performed…

- She succumbed following status epilepticus…and autopsy was performed





Neurocysticercosis presenting as organic brain syndrome and dowry death. NIMHANS Journal 1993;11: 137-9

Psychiatric symptoms and NCC

- Association is now well recognised
- Cause……? Neuroanatomical location at grey-white junction causing deafferentation/synaptic dysfunction
- Neurotransmitters
  - Acetycholine rich areas
  - Disturbance of serotonin metabolism by the parasite

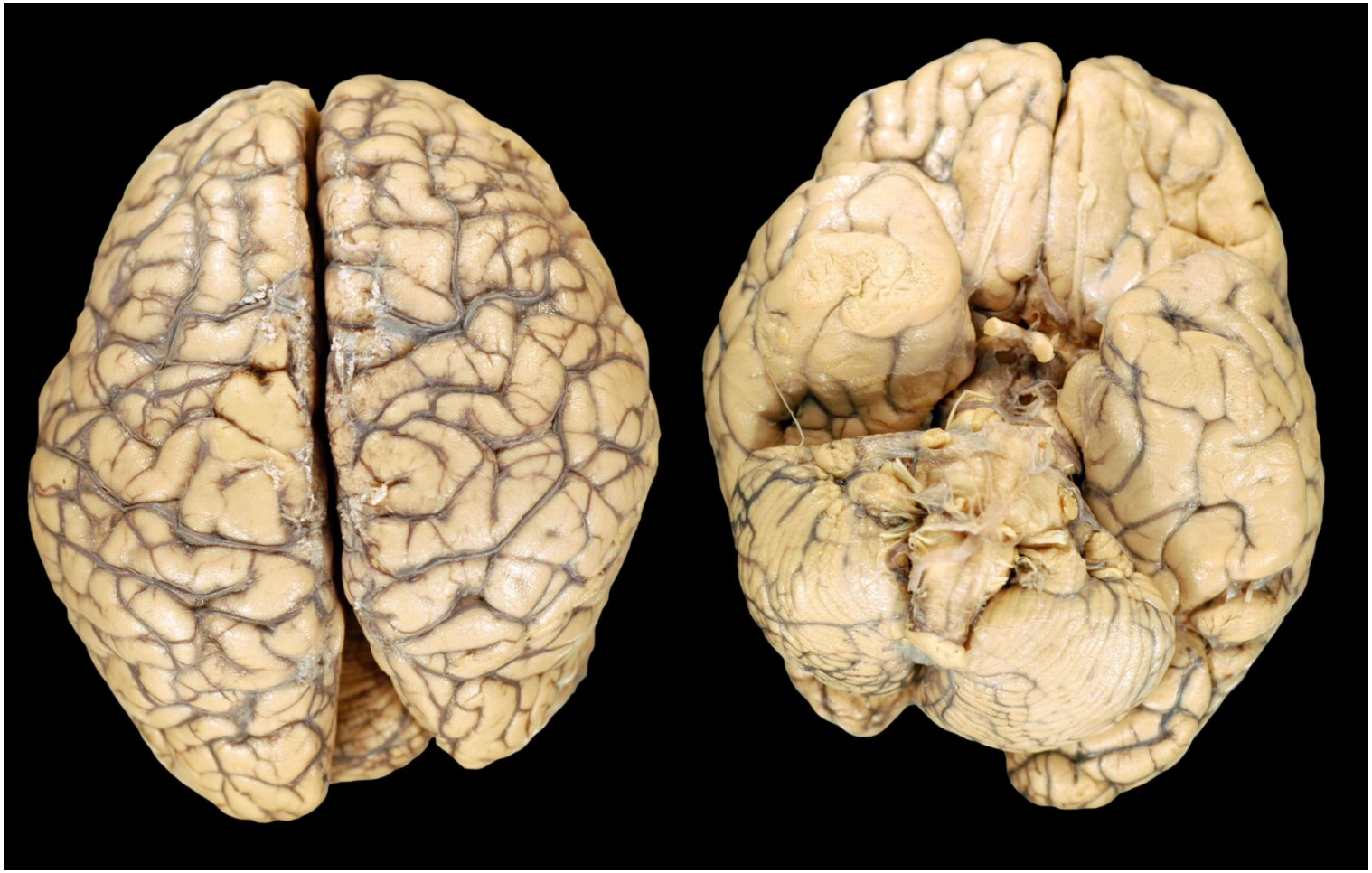
Case 2

His-story (Case 2)

- 50 year old tailor, brought to our psychiatric service with complaints of sleeplessness, restlessness, wandering tendency, irrelevant talk, negligence of food and personal hygiene, abusive and assaultive behaviour of five days duration. He had fever, two days prior to the onset of his symptoms.
- During the past six months. he was found to be progressively withdrawn, losing interest in work, and occasionally complaining of mild headache.

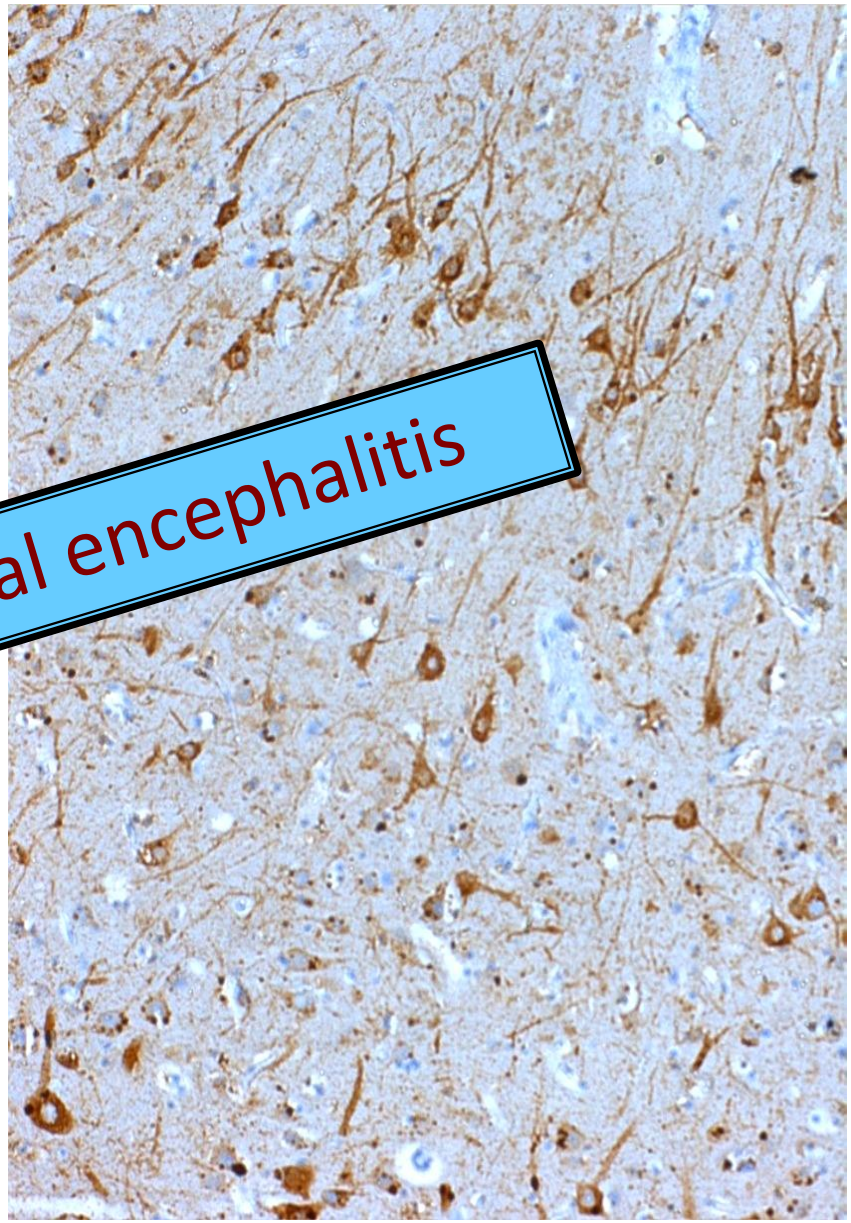
On admission (Case 2)

- On examination, he was afebrile.
- Appeared ill-kempt man with increased motor activity, actively hallucinating, talking irrelevantly and expressing persecutory ideas that he was going to be 'shot' by his relatives
- Investigations including CSF analysis was normal.
- Admitted with a diagnosis of schizophrenia and started on Chlorpromazine 500mg per day
- Over the next four days, he deteriorated in sensorium and succumbed after four days.
- Autopsy was requested…..



Brain at autopsy – no edema, no hemorrhages….

Rabies viral encephalitis



Immunohistochemstsry: widespread antigen

Rabies viral encephalitis…learning

- Presenting with predominantly psychiatric/ behavioural symptoms is rare
- Six cases in last 20 years: Schizophrenia, delerium tremens, acute psychosis, hypomania and hysteria
- Absence of history of dog bite, hydrophobia, aerophobia

Rabies masquerading as psychiatric diseases- a clinical study. Shankar SK, Goswami U, Madhusudana SN. APCRI 200;1:46-49

Why psychiatric manifestations?

- High incidence of rabies in our country, hence high index of suspicion essential
- Herpes simplex virus (HSV) encephalitis - behavioral and psychiatric manifestations very similar to rabies.
- Preferential anatomic involvement oflimbic system- hippocampus, amygdala, temporal cortex, hypothalamus, and cerebral cortex explains similar clinical manifestations, leading to confusion in diagnosis.
- Cholinergic, serotoninergic pathways

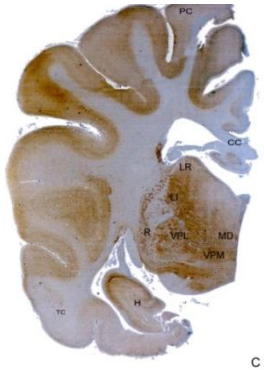
Introspection…

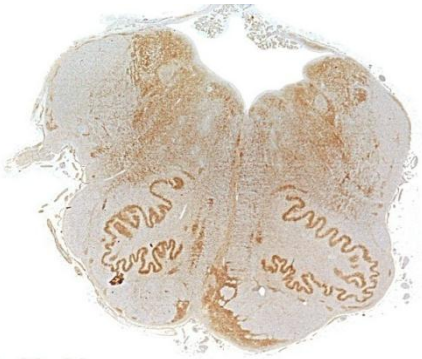
- Common to all – symptomatology due to involvement of the limbic system by viral antigen

Cerebral Cortex (cingulate, insular)

Hippocampus

Basal ganglia
Thalamus
Hypothalamus
Amydgala



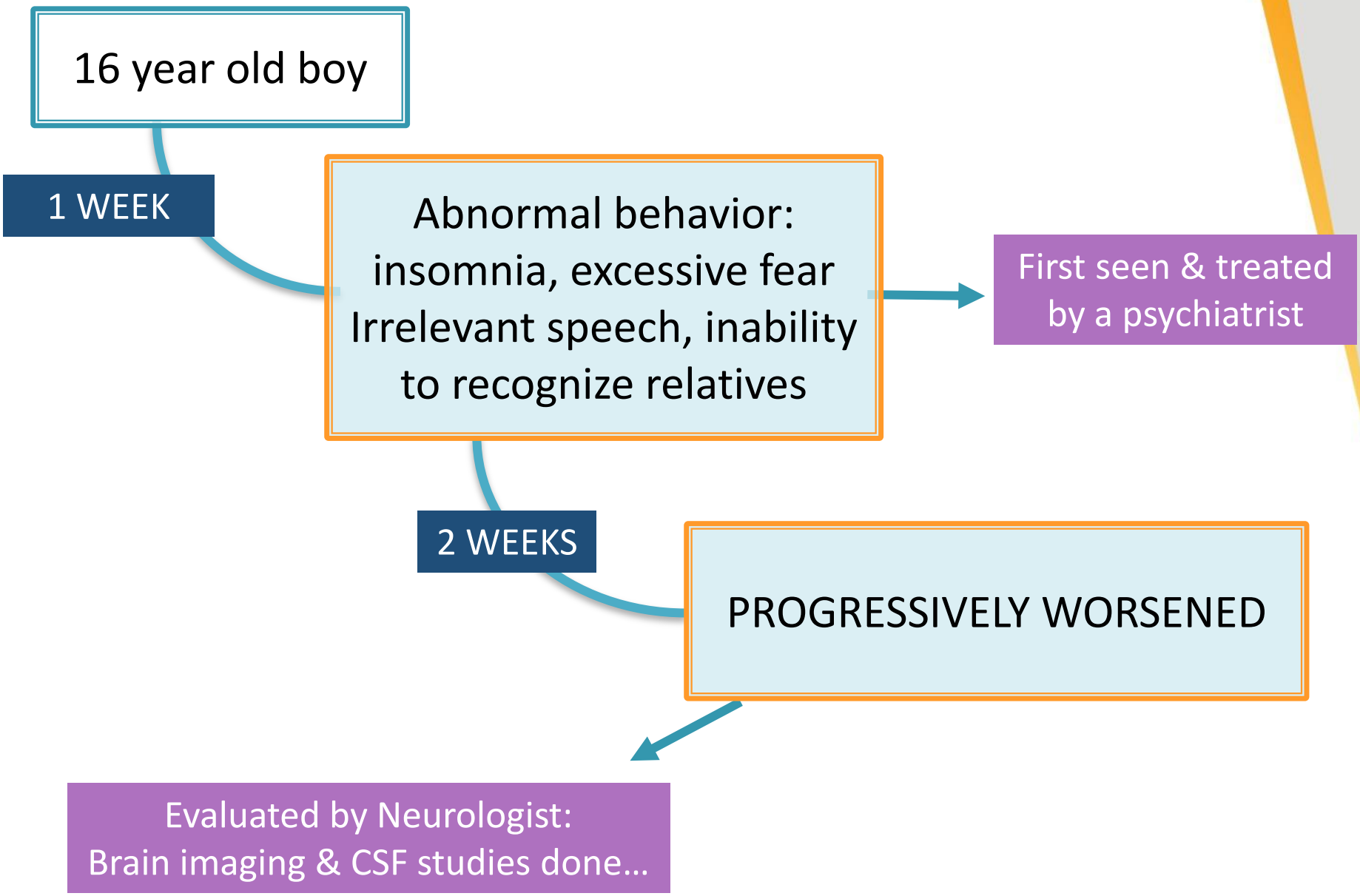


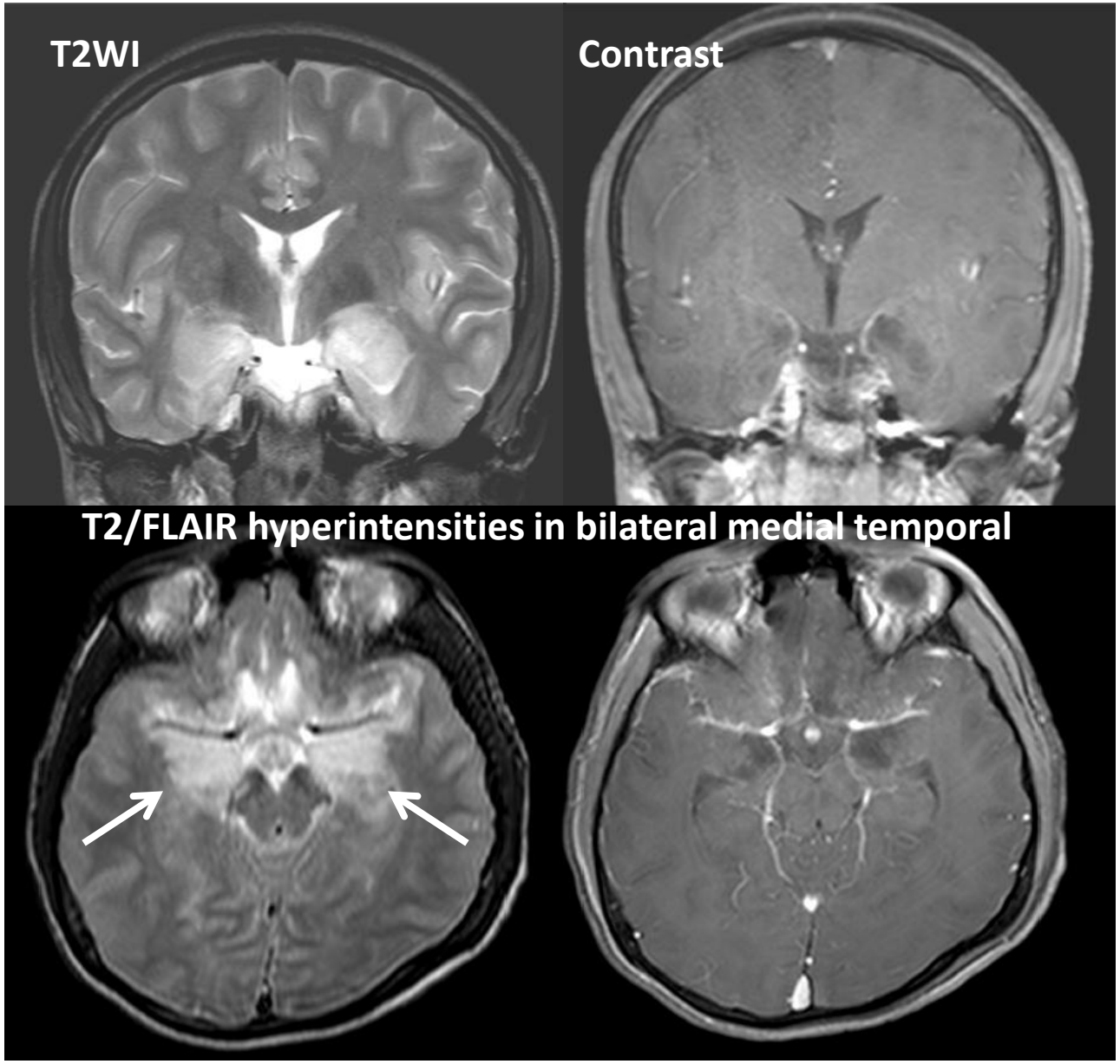
Medulla
idline raphe nuclei

Infections and schizophrenia?

- Epidemiological studies suggest infectious agents may be implicated in causation
  - Prenatal infections (Influenza epidemic - 1988)
  - Endogenous retroviruses
  - HSV, CMV
  - Toxoplasma gondii
  - Borna virus
- Neurodevelopmental hypothesis – interferes with neural development
- Autoimmune process due to molecular mimicry?

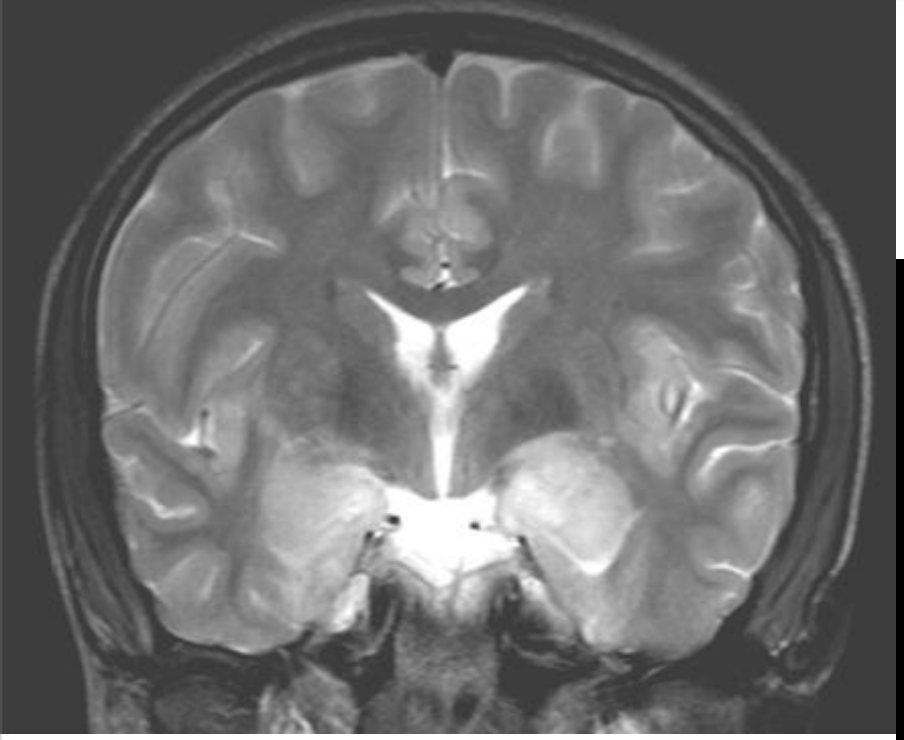
Case 3


16 year old boy
1 WEEK
Abnormal behavior:
insomnia, excessive fear
Irrelevant speech, inability
to recognize relatives
First seen & treated
by a psychiatrist
2 WEEKS
PROGRESSIVELY WORSENED
Evaluated by Neurologist:
Brain imaging & CSF studies done…

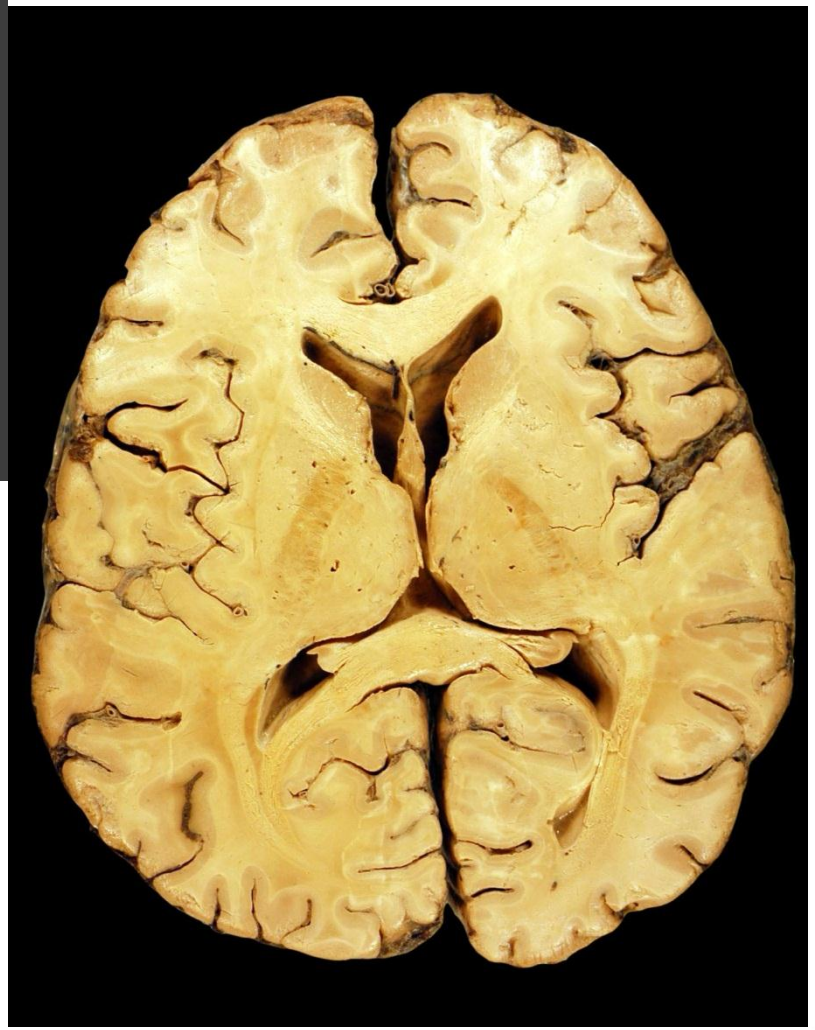


HSV encephalitis
Rx – Acyclovir
Improved…

4 weeks later returned with behavioural symptoms
CSF – HSV negative…Progressively deteriorated



MRI: bilateral median temporal hyperintensities.



No hemorrhages…

No necrosis!

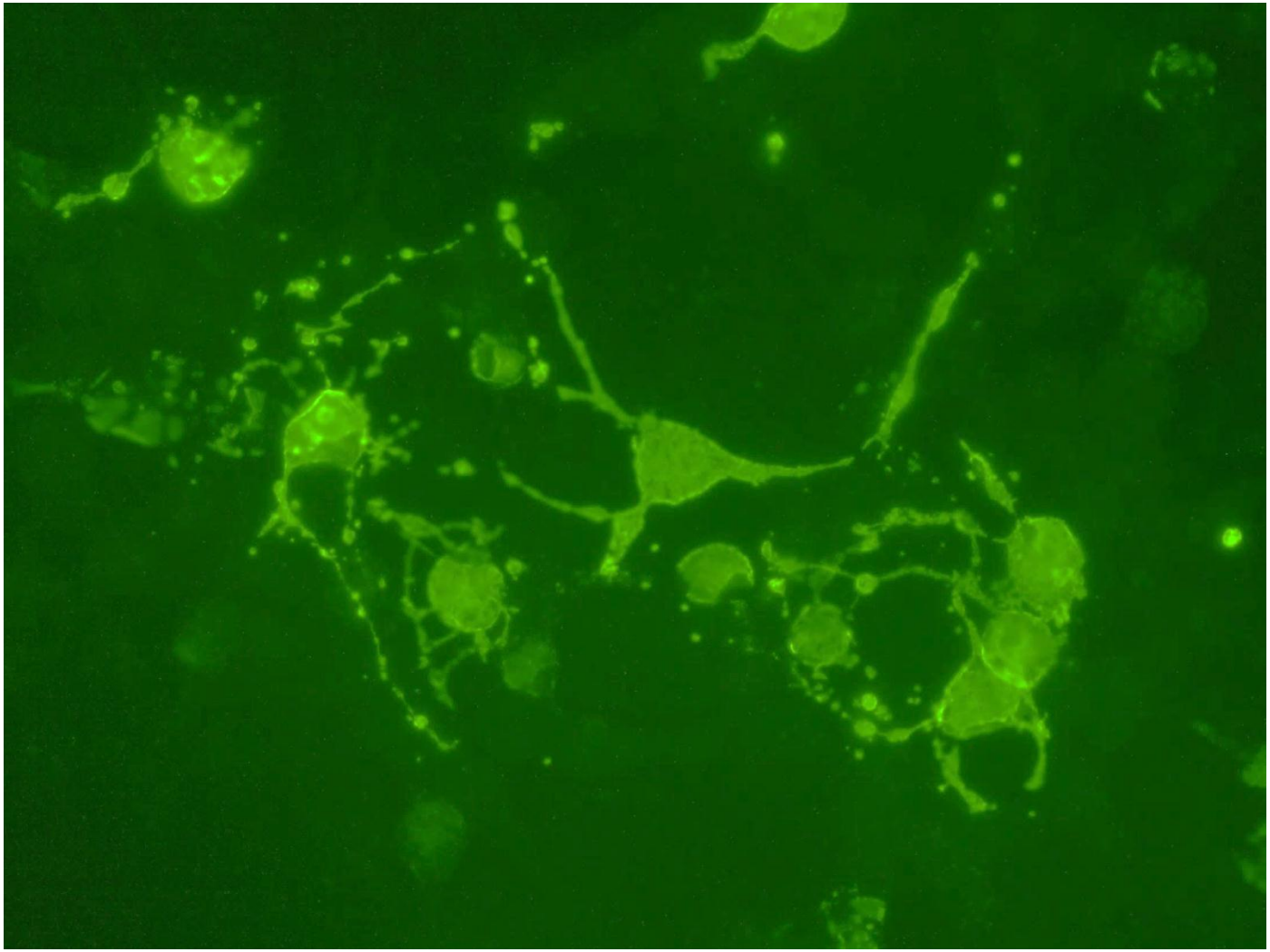
No HSV inclusions, but mild inflammaton

Post HSV encephalitis

Usually occur a few weeks after viral therapy and represent either

- A true viral relapse of HSVE (CSF PCR positive for HSV, new necrotic lesions on brain MRI, and response to acyclovir therapy) or
- A disorder postulated to be immune-mediated (CSF negative for HSV, no new necrotic lesions, and no response to acyclovir).

NMDA positive



Our experience of NMDA R encephalitis in children

- NMDA – 60/427 (14%) positive
- Most common psychiatric symptoms at presentation were crying spells and anger outburst, episodic screaming, fearfulness, social withdrawal, decreased appetite and decreased sleep.
- Decreased speech output and speech comprehension as well as failure to recognise familiar people .
- Involuntary movements like choreiform movements, dystonia and posturing was also noted.
- Almost all cases had generalised tonic clonic seizure.
- Psychiatric symptoms improved within 6 months of treatment.
- Most common psychiatric diagnosis ?mood disorder ?Psychosis

Case 4

62-year-old housewife, right-handed

- Burning Paresthesias: (2 years)
- Distal lower and upper limbs, symmetrical
- Dipping extremities in cold water provided relief
- Subsided spontaneously after two months

- Reduced interaction, reduced activity (1.5 years)
- Crying spells

- Impaired memory (1 year)
- Frequently misplaces her things
- Repeatedly asks same questions
- Forgets to cook for family

62-year-old housewife, right-handed

- Disinhibition (1 year)
- Voids outside the home
- Incontinence: Not concerned

- Abnormal behavior (1 year)
- Silent, reduced interaction
- Anger outbursts, shouting when spoken to
- Abusive language, using slangs

Hallucinations
Myoclonus, seizures
} ABSENT

- Family history: sudden death in brother at 47 years
- Patient's education: 3rd standard

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NEUROLOGICAL EXAMINATION

Conscious, disoriented, no eye-to-eye contact
Speech: mute
MMSE: not done

Motor system: Generalised wasting, increased tone & normal stretch reflexes

Release reflexes: Present

Sensory & cerebellar: could not be assessed
Gait: slow, with short steps

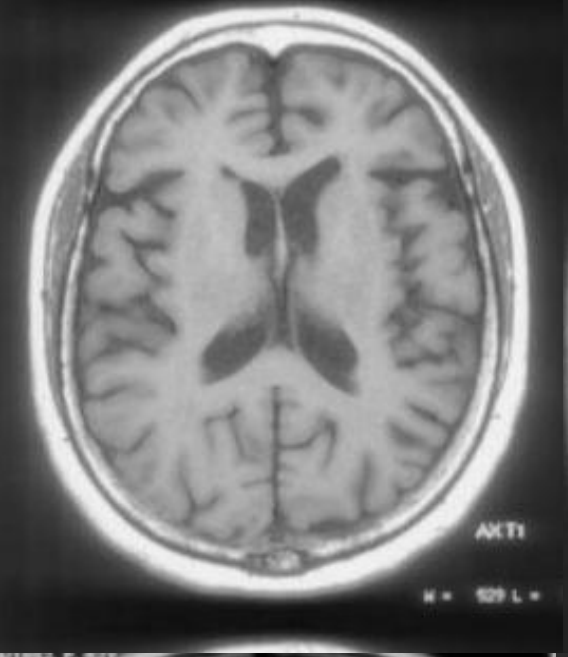
Investigations

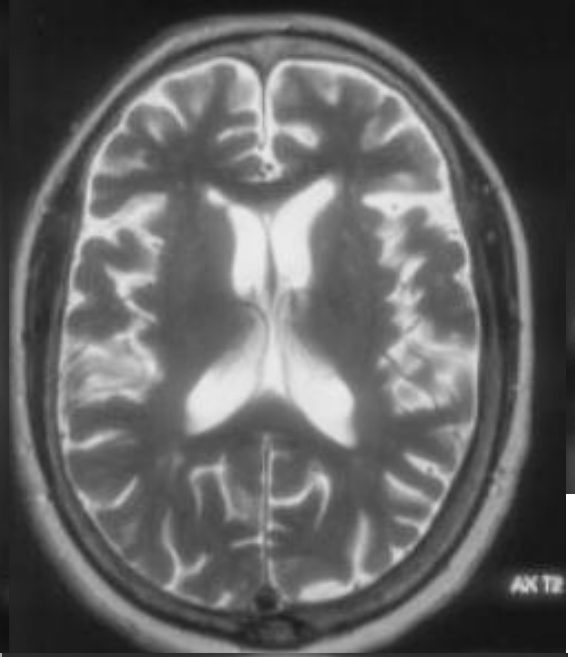
Normal

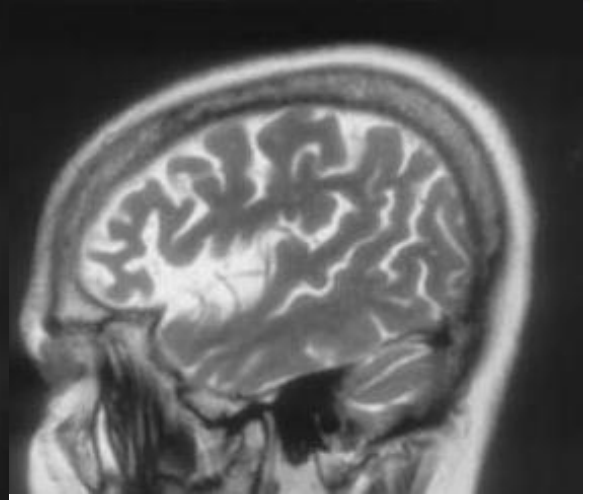
Hemogram
Liver & kidney function
Thyroid functions
VDRL, HIV
CSF routine
B12: 247 (ref: 180-914 pg/ml)

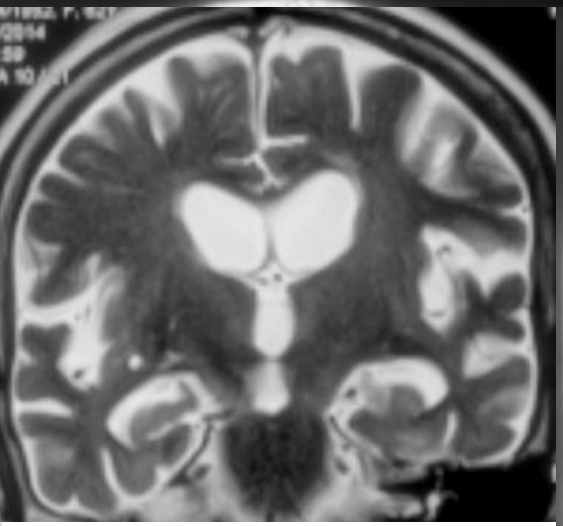
Abnormal

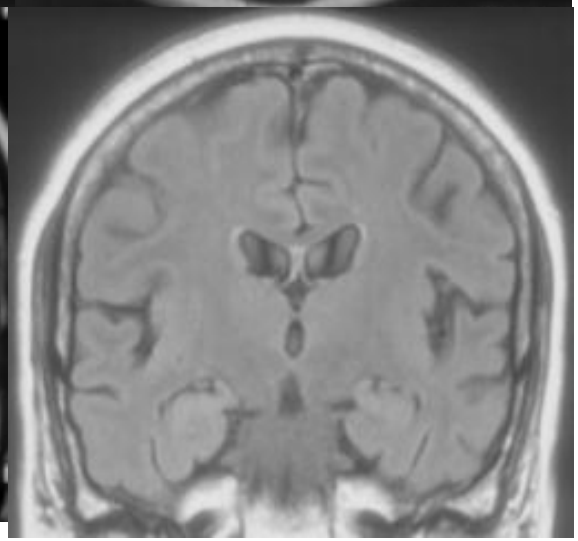
ESR: 66
Blood sugar: 226











Frontal & Peri sylvian atrophy
Hippocampi – mild atrophy

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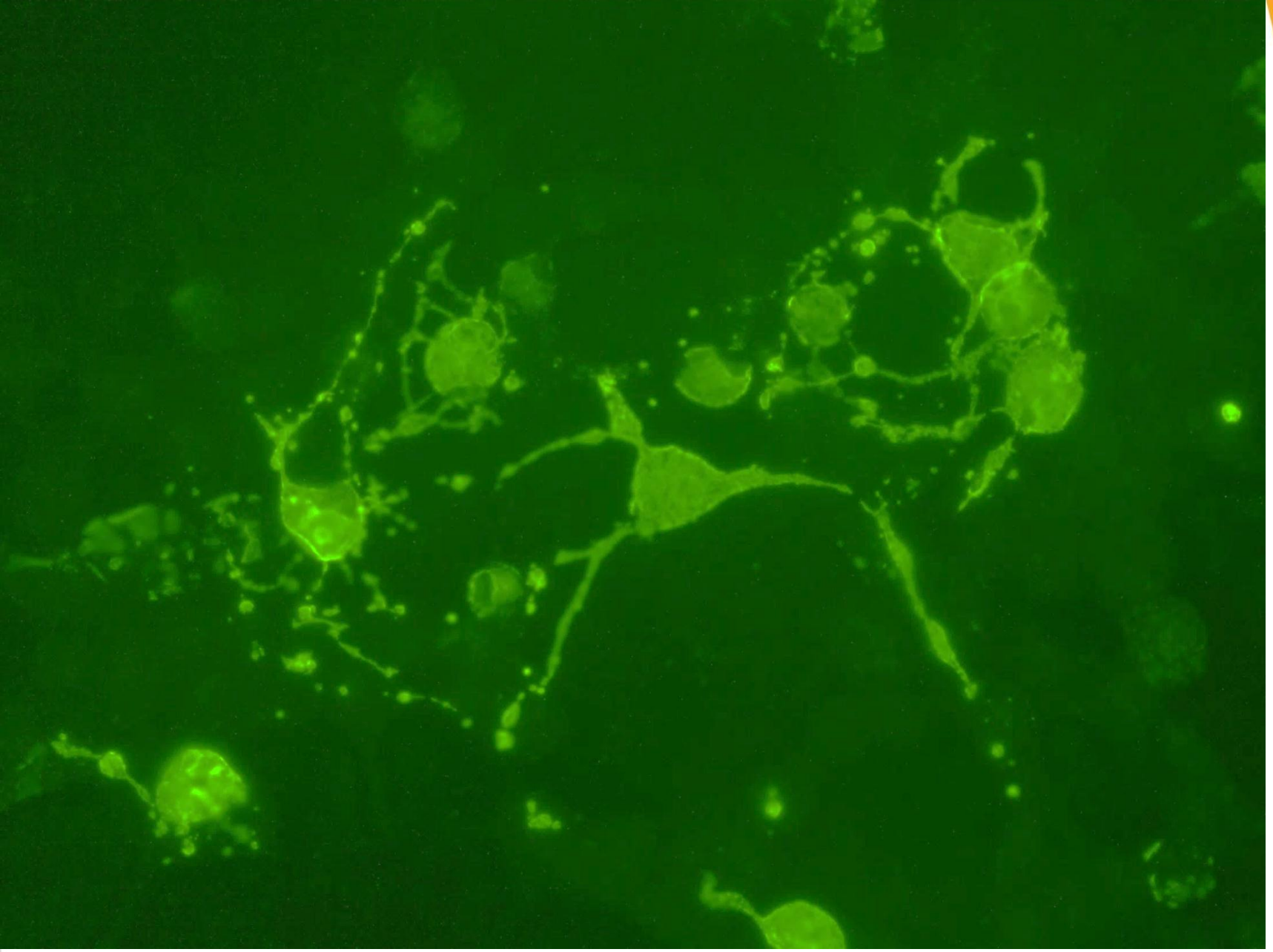
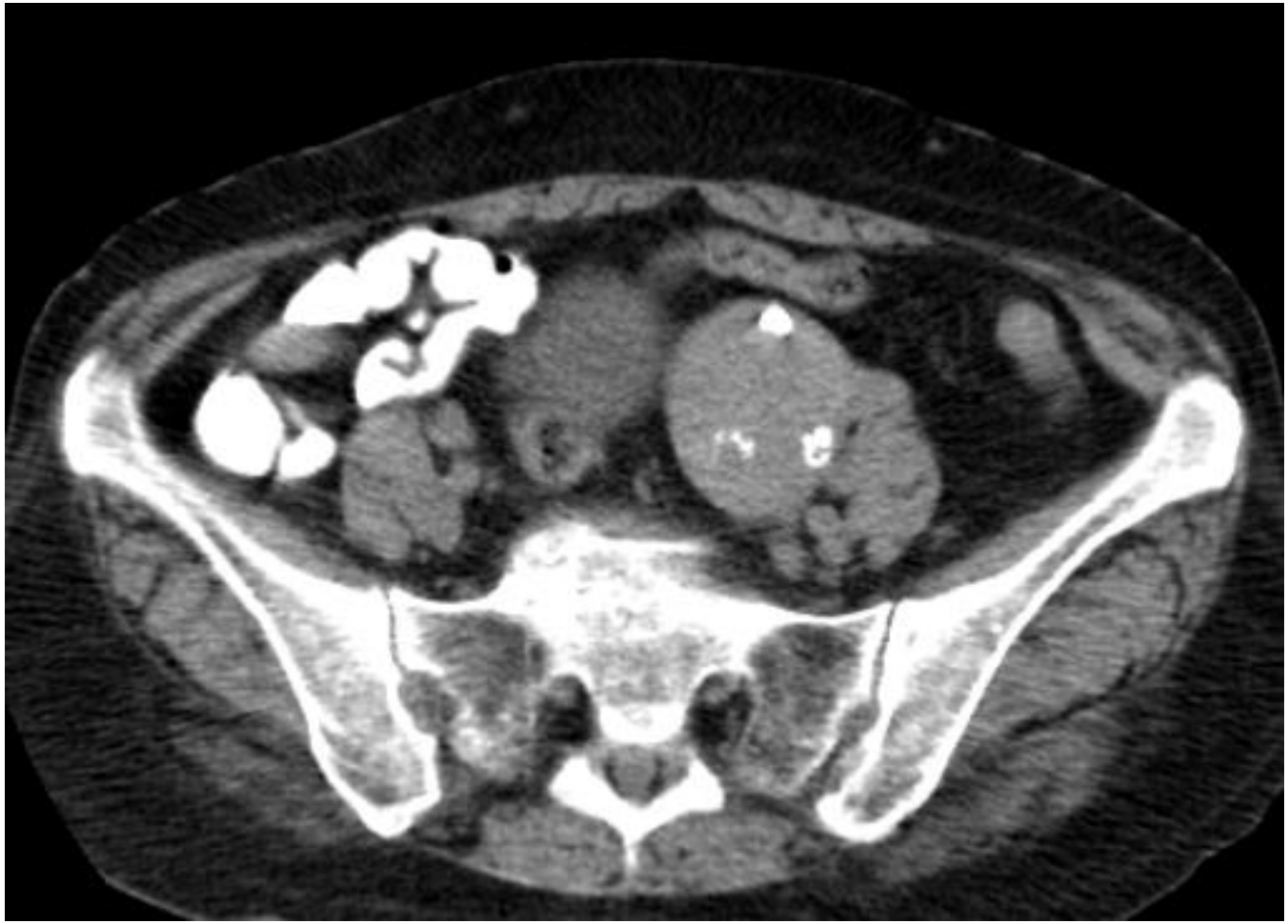
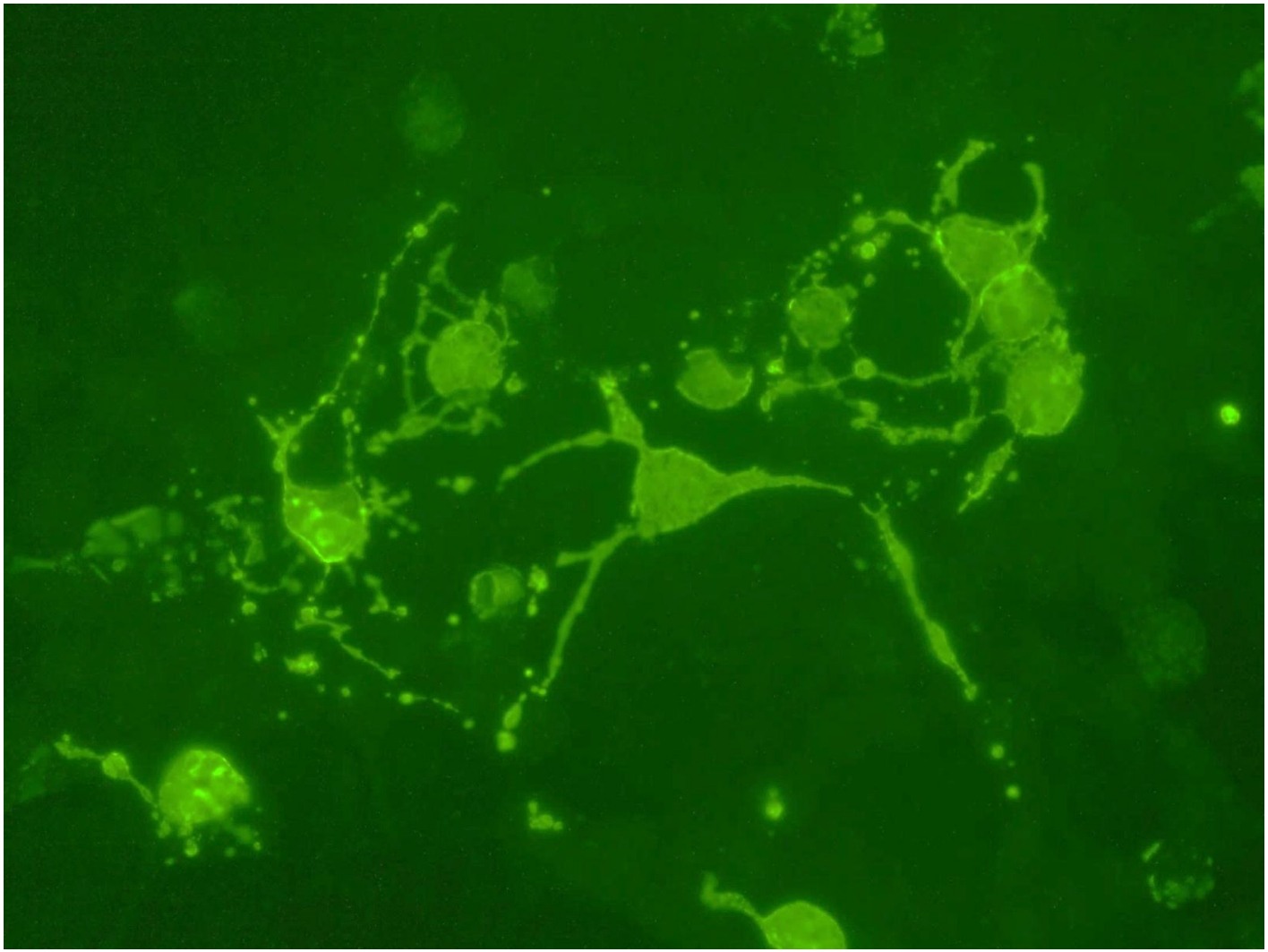


Abdominal CT



VGKC positive



Learning ?

- Exclude autoimmune if behavioural symptoms dominate & relatively rapid progression, involuntary movement, seizures
- Paraneoplastic/non-paraneoplastic

Case 5

Her-story

- 65-year-old woman was referred for evaluation of rapidly progressive dementia
- Progressive cognitive impairment, abnormal behavior, slurred speech, inability to carry out activities with right upper limb, gait disturbances, emotional lability, and double incontinence that evolved over the last 8 months.
- There was no myoclonus or seizures.

Her-story contd…

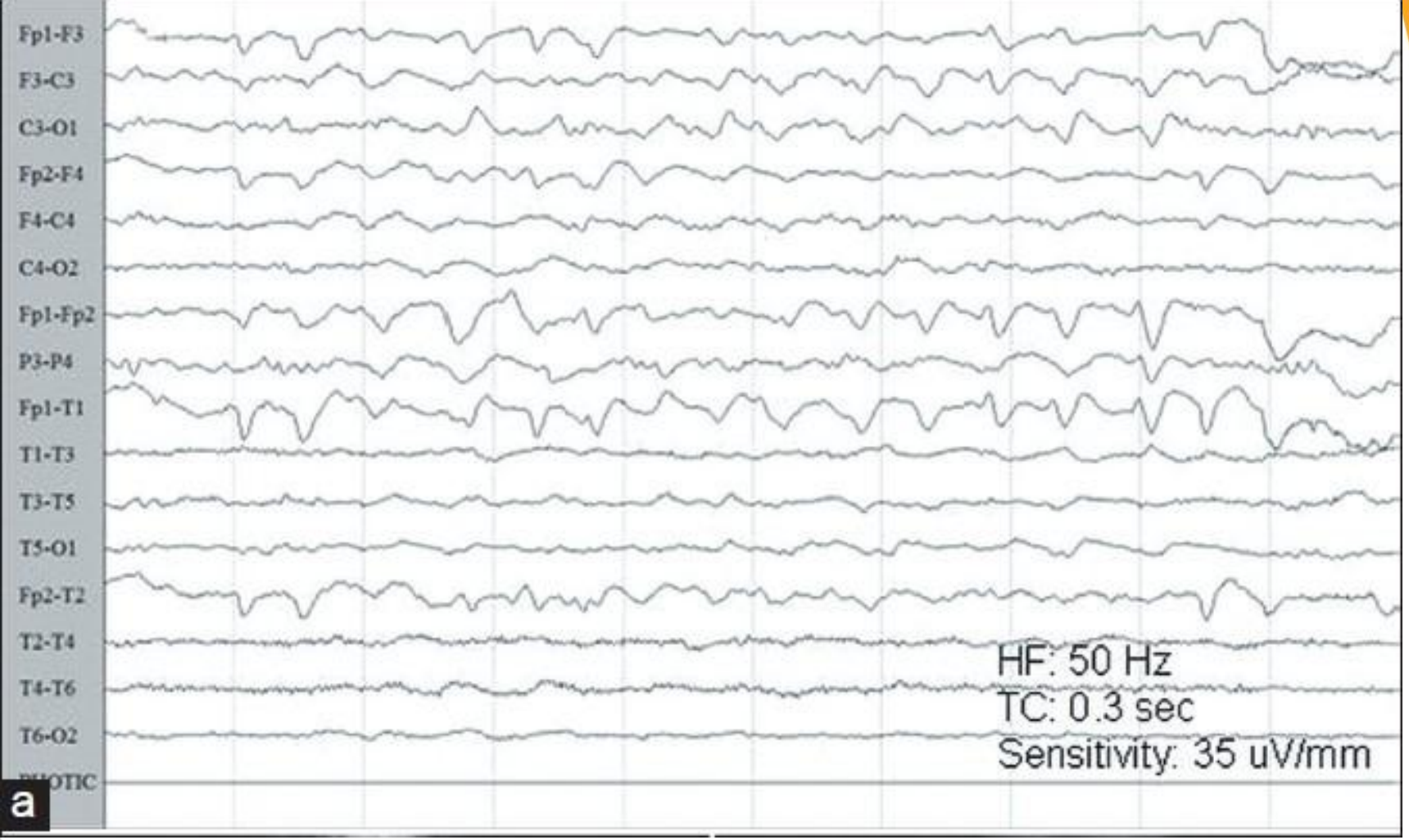
- Non-vegetarian consuming egg, fish, and meat products.
- Underwent surgery for lipoma on the chest wall several years ago
- Detected to have hypertension five years ago and on anti-hypertensive medications.
- No family history of dementia.

On/examination …

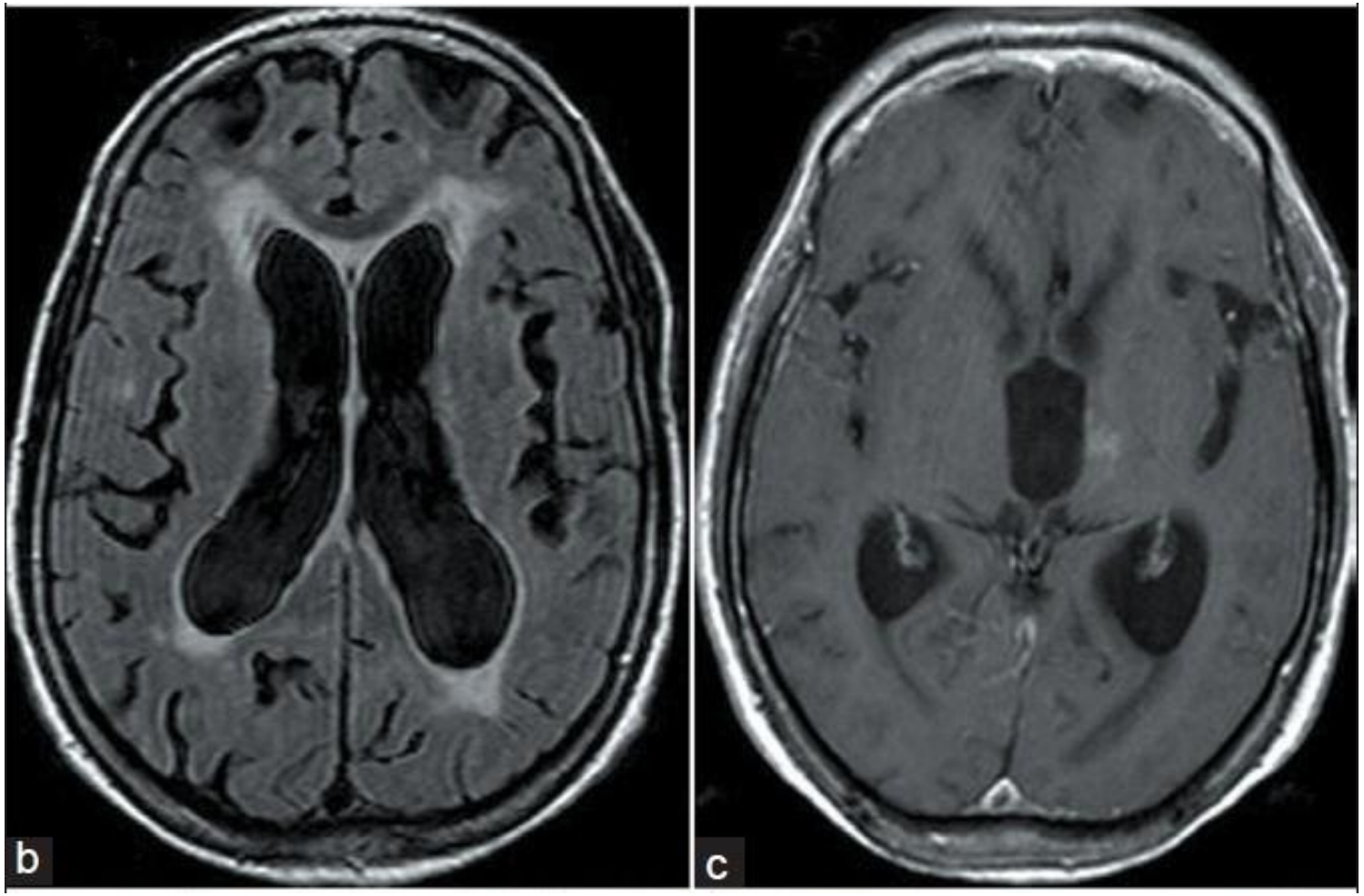
- Vitals signs -normal.
- Conscious, and cooperative but could but not verbalize, spontaneously or on commands.
- Profound cognitive impairment. Could not comprehend and communicate and hence MMSE/ detailed neuropsychological assessment could not be carried out.
- Exhibited frequent unprovoked laughter.
- Rigidity in all four extremities, decreased blink rate, bradykinesia, and required one person support while walking.
- Other systemic examination and per vaginal and rectal examination were unremarkable

Investigations…

- Routine urinary, hematological, biochemical (including liver and renal function) assays were normal.
- Serum levels of thyroid hormone, anti-thyroid globulin, ammonia, and vitamin B_{12} were within normal limits.
- Serological tests for vasculitis (RA factor, ANA), syphilis and HIV were negative



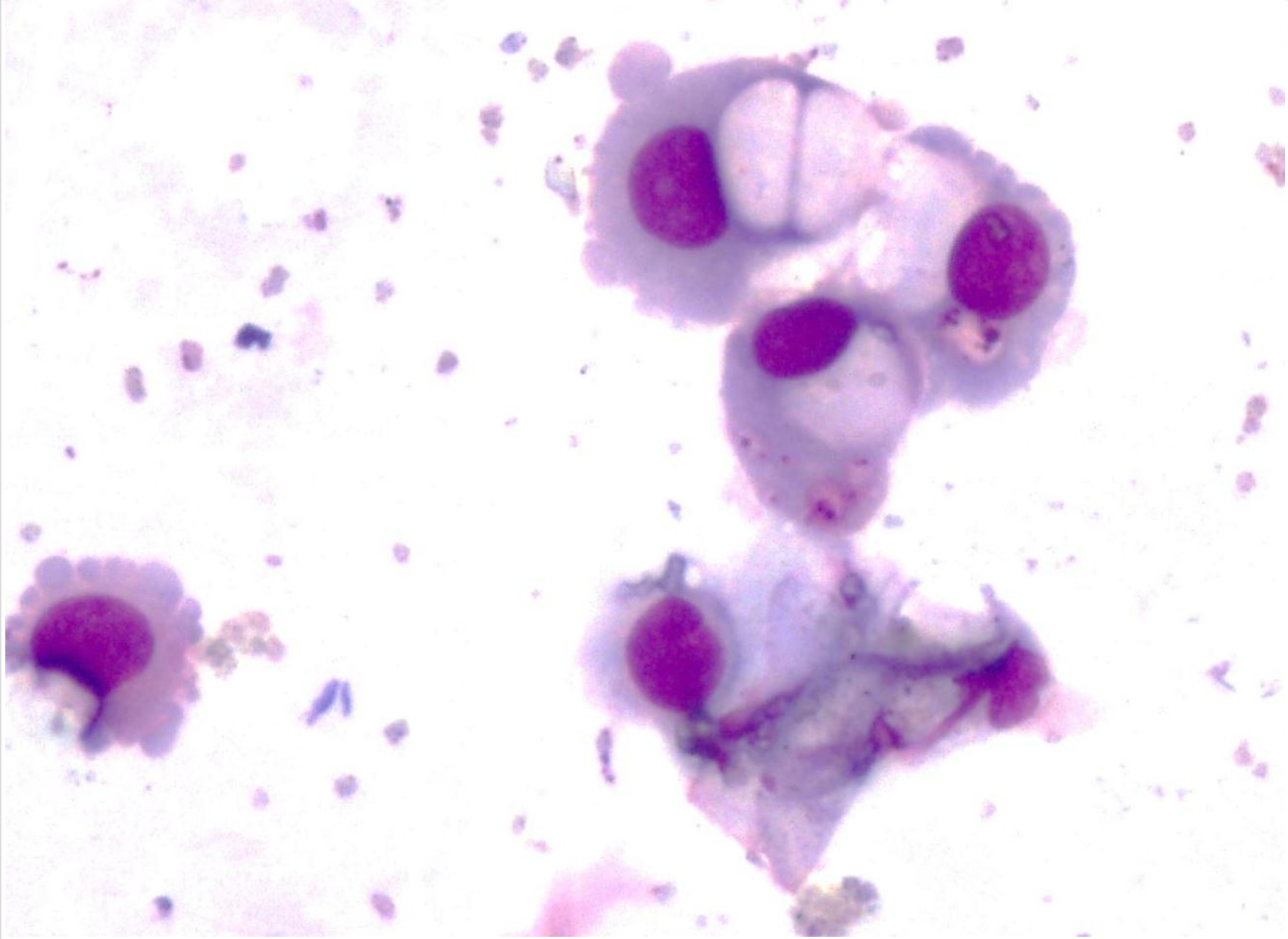
- Scalp EEG -periodic biphasic and triphasic broad complex sharp waves occurring at 0.5–1.5 Hz frequency in both fronto-temporal leads (left>right)

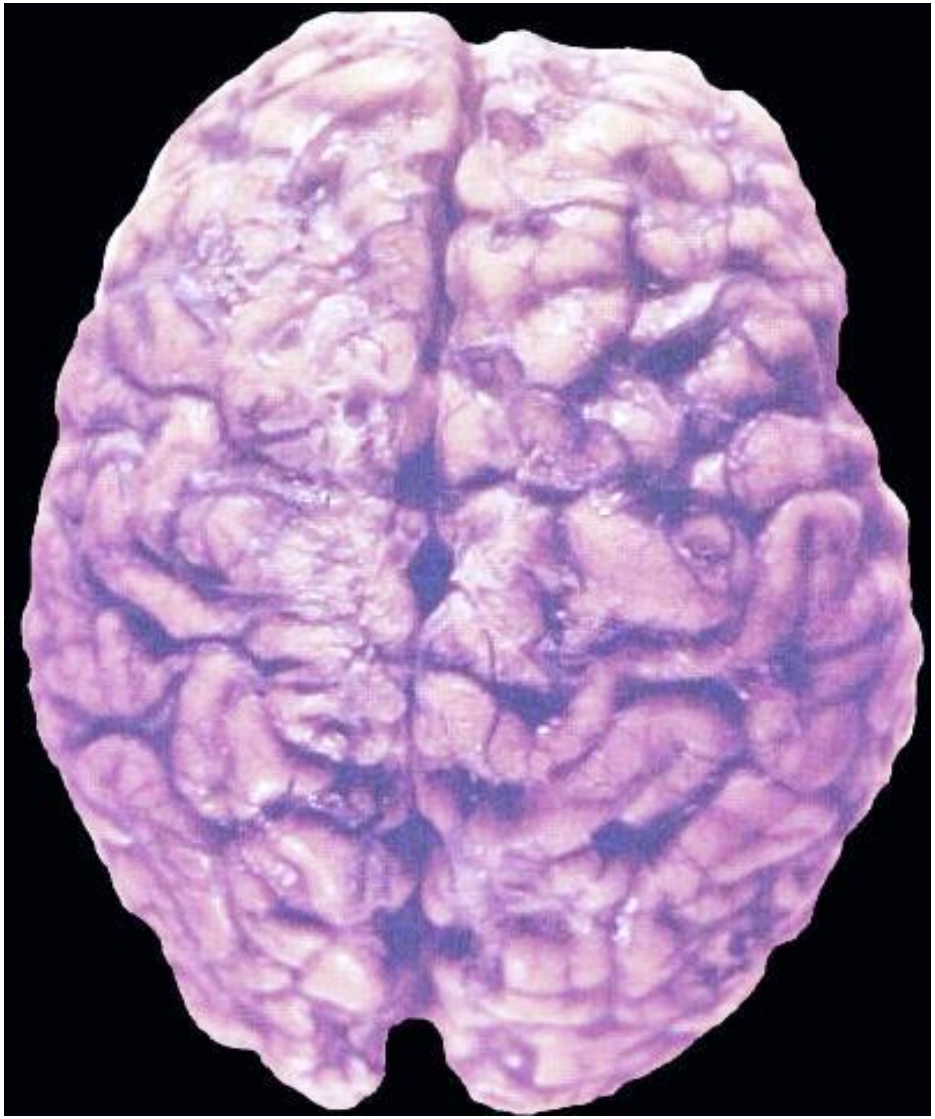


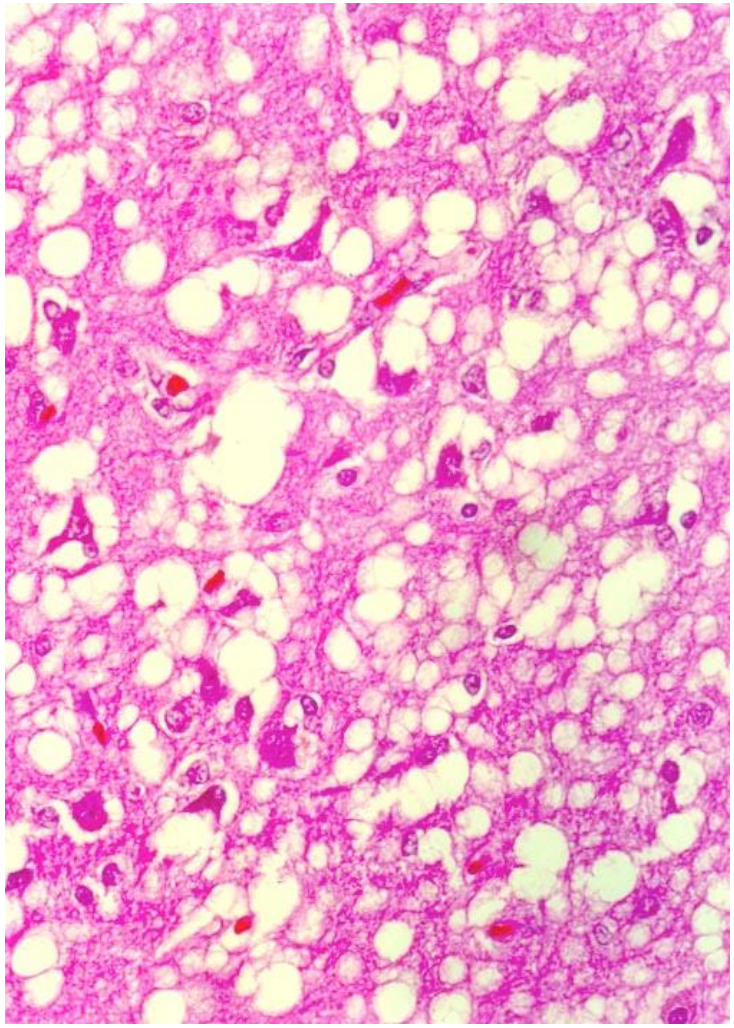
- Axial MRI of brain -cortical atrophy and peri-ventricular changes

Other investigations…

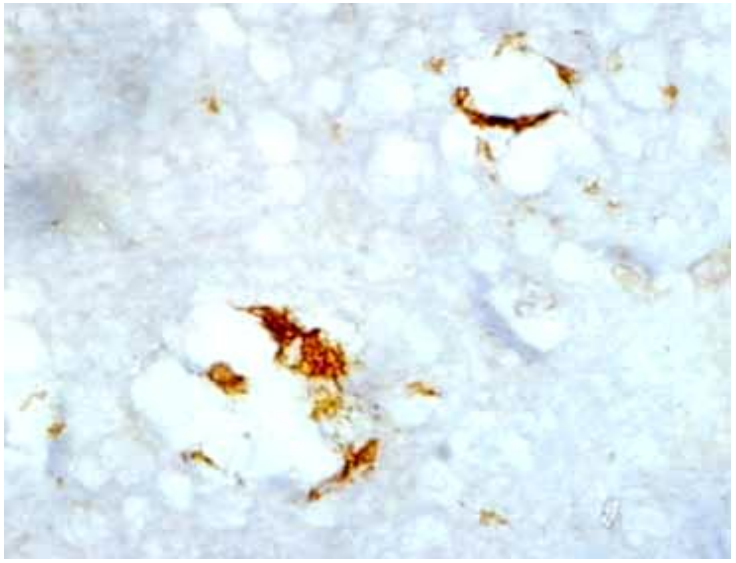
- Carotid and vertebral artery Doppler study was normal.
- CSF -clear, colorless, protein - 58 mg/dl (normal ≤ 45.0 mg/dl), sugar 47 mg/dl, and cell count of **14 cells/cu.mm**
- CSF-VDRL was non-reactive and negative for cryptococci.
- CSF could not be tested for 14-3-3 protein
- Internal malignancy screen, serum CEA level, bone scan, X-ray chest, Ultrasound of abdomen and colonoscopy were normal.

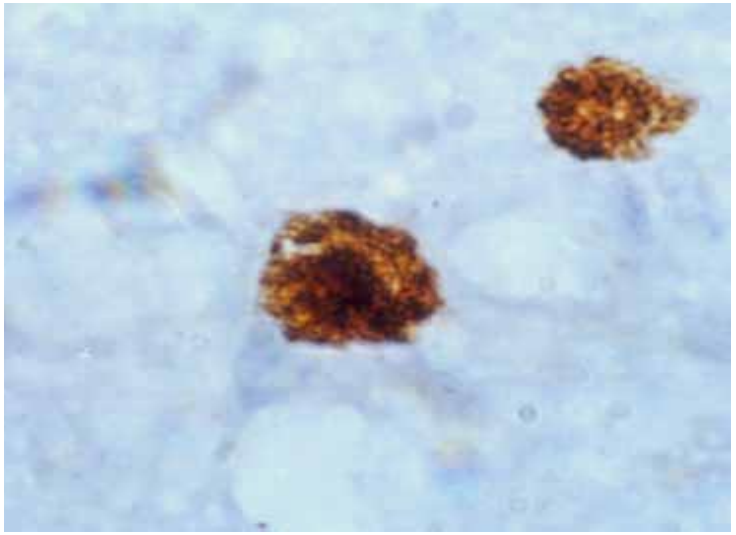






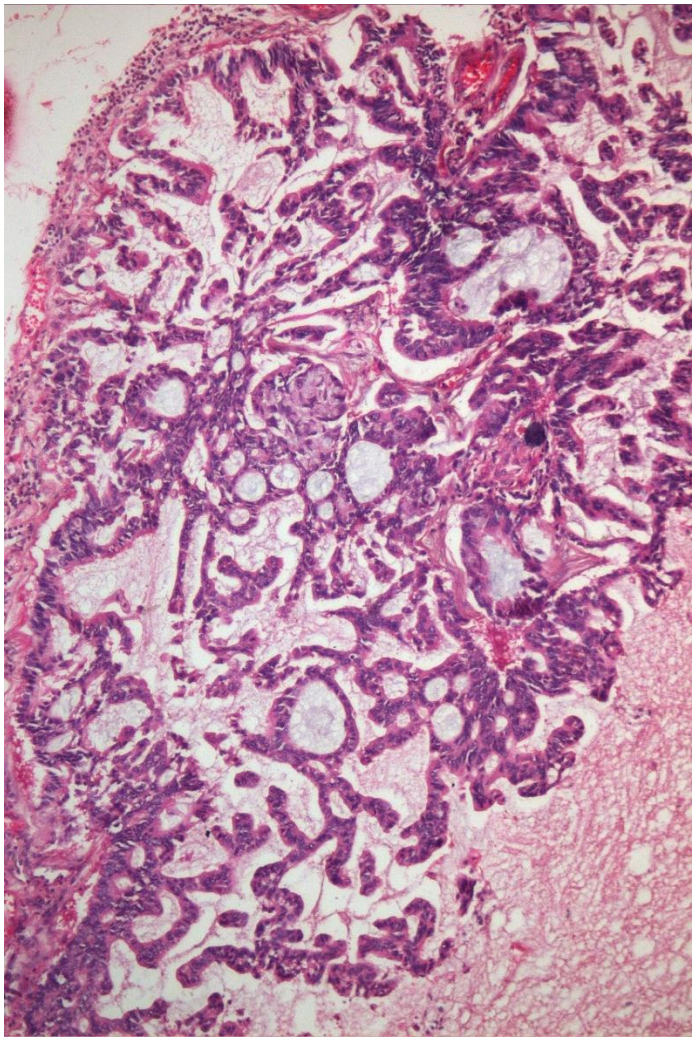
SPONGIFORM CHANGE IN GREY MATTER

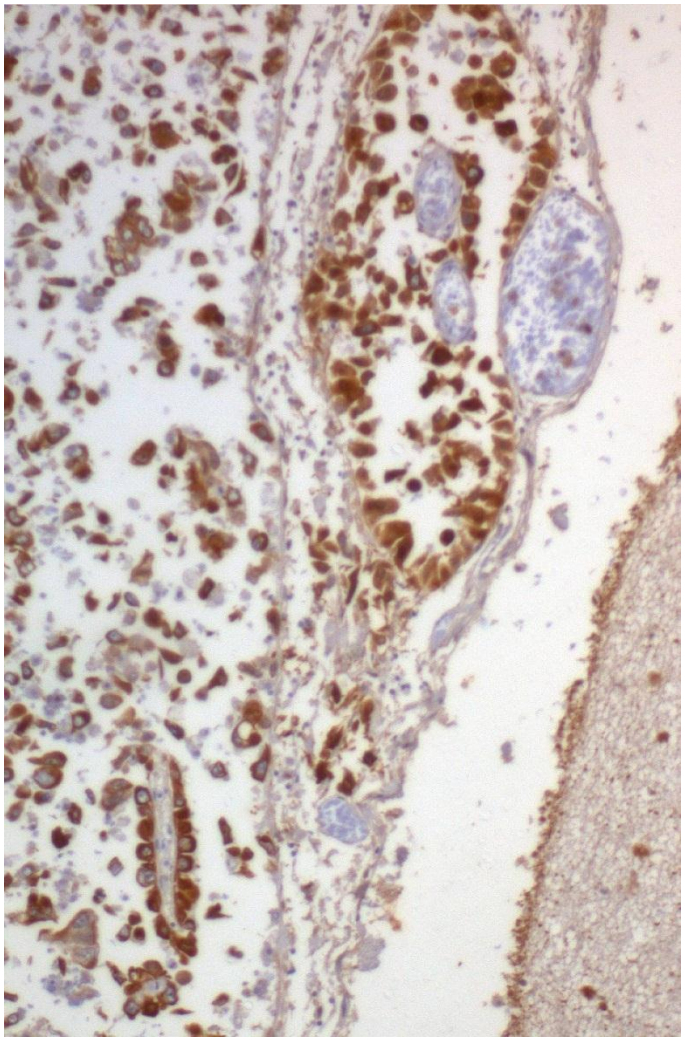




Prion plaques

Carcinomatous meningitis





Learning ....

- Dementia caused by diffuse carcinomatous meningitis and multiple cortical tumor nodules altering the CSF dynamics and deranged cortical activity.
- Topographic distribution of the lesions in frontal cortex, hippocampus, striatum account for dementia, and extrapyramidal symptoms.
- EEG alterations - due to multifocal disruption of the synaptic connectivity in the cortex by the tumor deposits.
- Only few reports of metastatic disease presenting like CJD is recorded in the literature.

Case 6

Case 6: “His”-story

- A 52-year-old gentleman working as a computer administrator in Sri Aurobindo Ashram, Pondicherry, presented with episodic sensation of fear of his colleagues at his workplace since February 2013.
- During these episodes, he reported being sad, perceiving a ‘dark’, ‘sinister’ energy within himself and negative feelings as though something bad was going to happen.
- He also became quarrelsome, and used to make irrelevant comments about his colleagues.
- His wife also noted that he would cry over simple issues and had poor stress management capability. He became slow in all activities.

Case 6:

- On 2nd October, 2013, he suddenly developed two episodes of seizures characterised by loss of consciousness, tonic posturing of the left sided limbs. He was admitted in a local hospital
- Post-ictally, he exhibited delusion of persecution and reference. He became aggressive, and had to be restrained with difficulty. He felt that he needed some ‘peace’ and ran away from the hospital to his friend’s house.
- Was started on sodium valproate, diphenyl-hydantoin and haloperidol. He discontinued treatment after a couple of months.
- Seizures recurred on 12th January, 2014. Sodium valproate and clobazam was re-initiated and referred to NIMHANS for further evaluation.

His-story continued

- No cognitive decline, except for amnesia in the peri-ictal period. No myoclonic jerks, ataxia, cranial nerve dysfunction, sensorimotor deficits, or autonomic symptoms.
- He scored 29 points on MMSE; could not tell the date correctly.
- Insight into his illness was absent. Judgemental capacity, abstract thinking, calculation, and memory were intact. No apraxias were noted.
- Cranial nerves, Motor system examination revealed normal power, tone, bulk and stretch reflexes. Plantar responses were flexor. There was mild bradykinesia in all limbs. Sensory and cerebellar systems were normal.

Immunological tests:

- Anti-nuclear antibody: 75.50 units (<20 negative; 20-60: moderate positive; >60 strong positive)
- ANA blot profile: anti SS-A positive +++

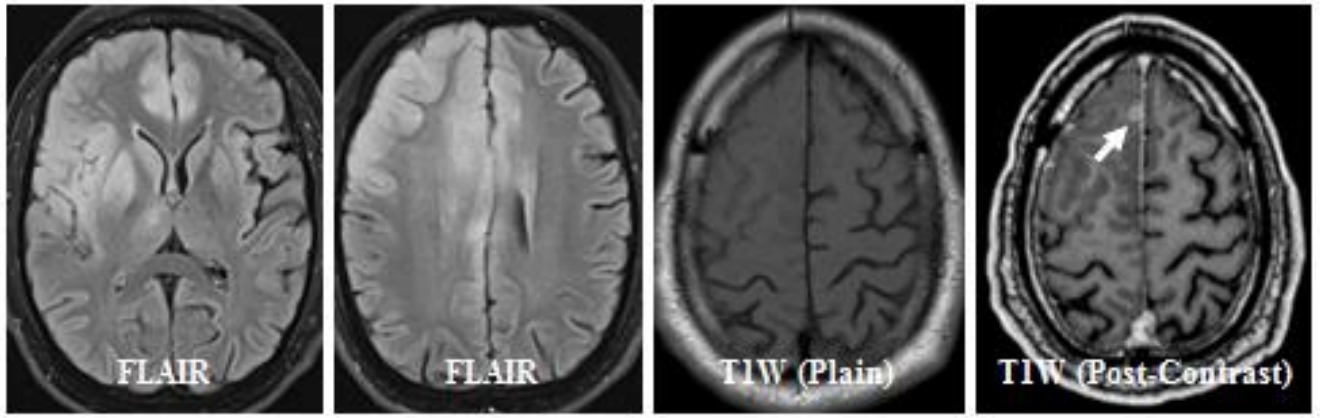
  Rest nRNP/Sm, Sm, Ro-52, SS-B, Scl-70, PM_Scl, Jo-1, CENP B, PCNA, dsDNA, nucleosomes, histones, ribosomal-P protein, AMA-M2, Mi-2, Ku: negative
- c-ANCA: 9.88 units (<20 negative; 20-30: weak positive; >30 strong positive)

  p-ANCA: 6.25 units (<20 negative; 20-30: weak positive; >30 strong positive)

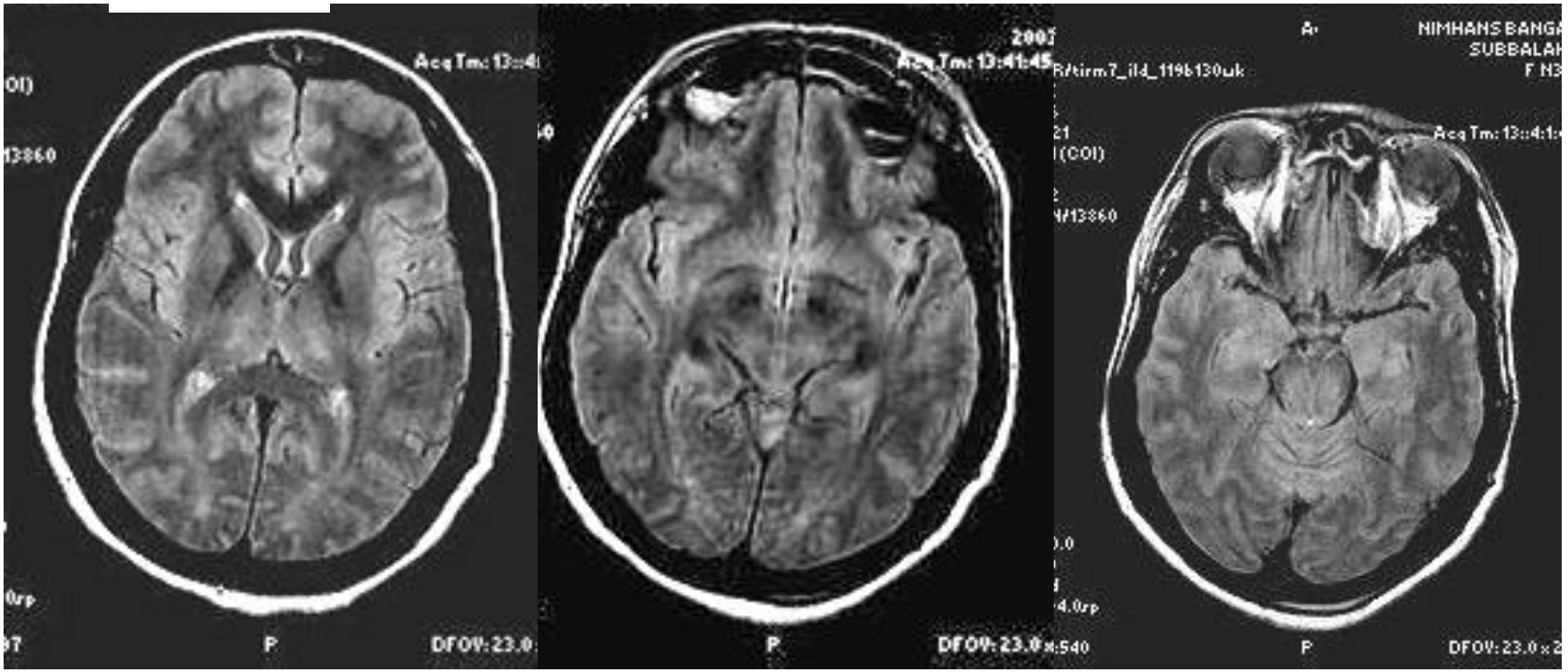
Autoimmune encephalitis panel

- VGKC (LGI1 & CASPR-2) negative by indirect immunofluorescence in serum
- **NMDA:** negative by indirect immunofluorescence in serum

March 2014

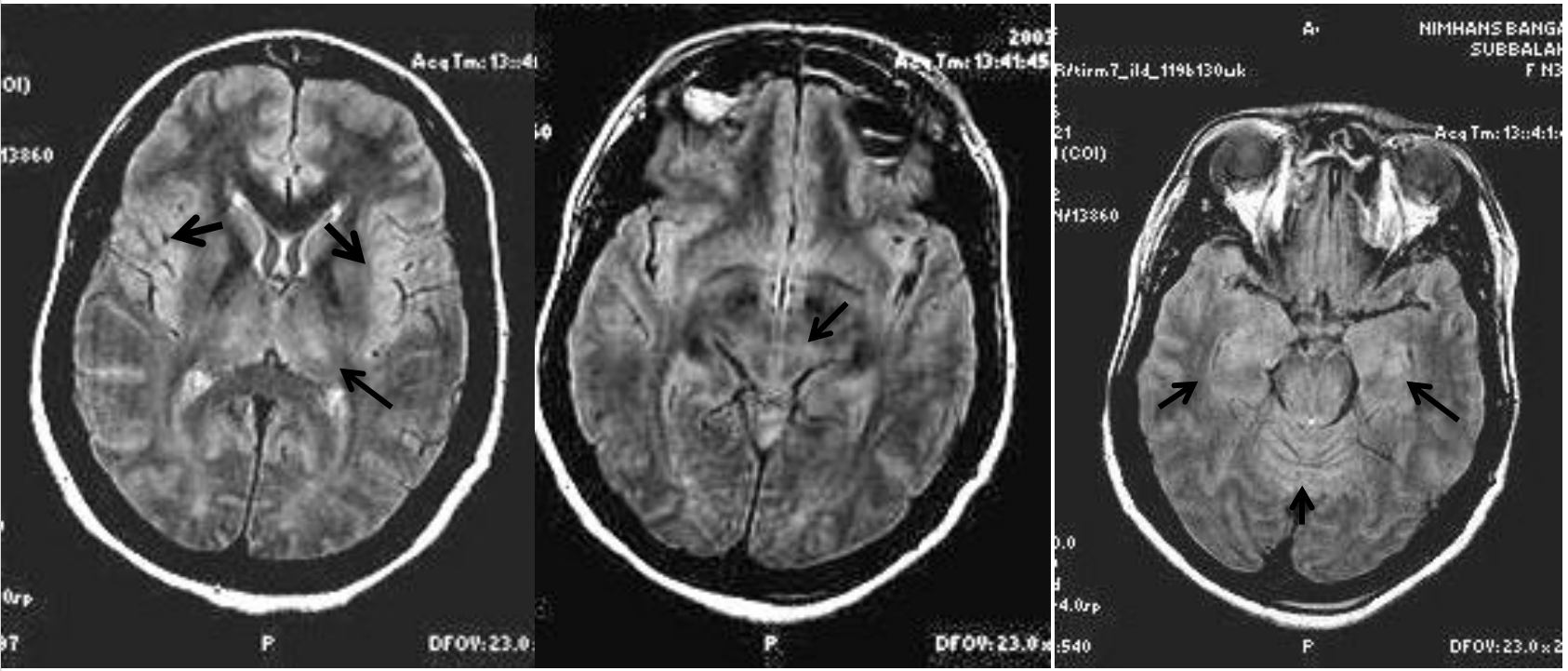


July 2014

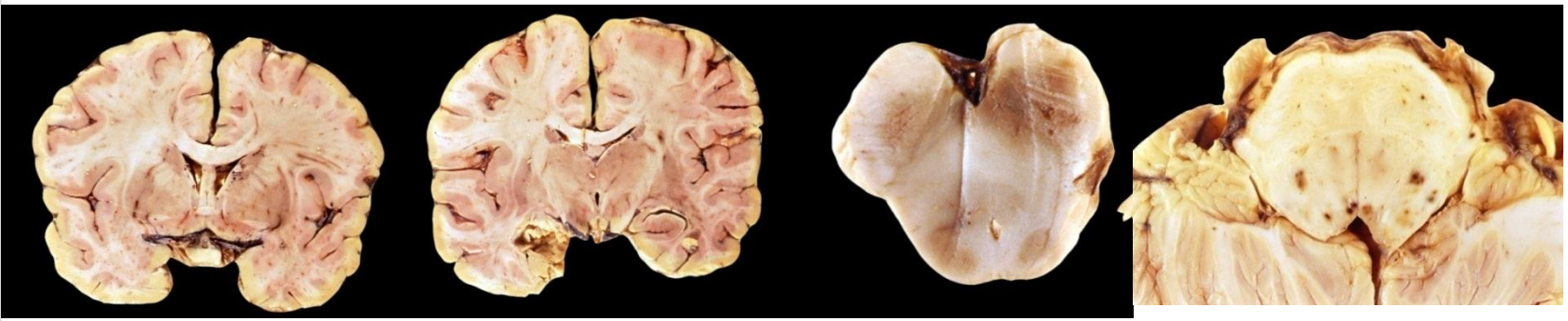


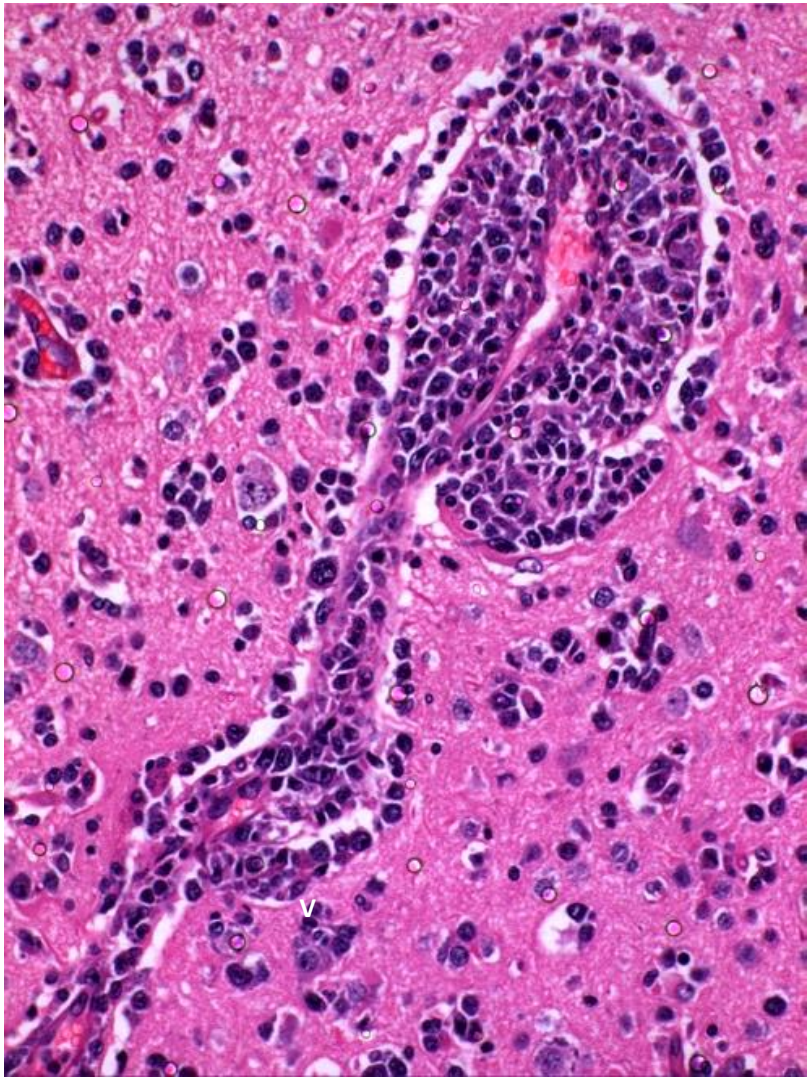
Course …

- The patient was seen in April, 2014, and given the option of empirical treatment with intravenous methyl prednisolone vs serial follow up. He opted for the latter.
- Deteriorated and expired after 1 month



MRI (DAY 8, 5 days prior to death)– hyperintensities in bilateral insular, medial temporal, thalami, brain stem

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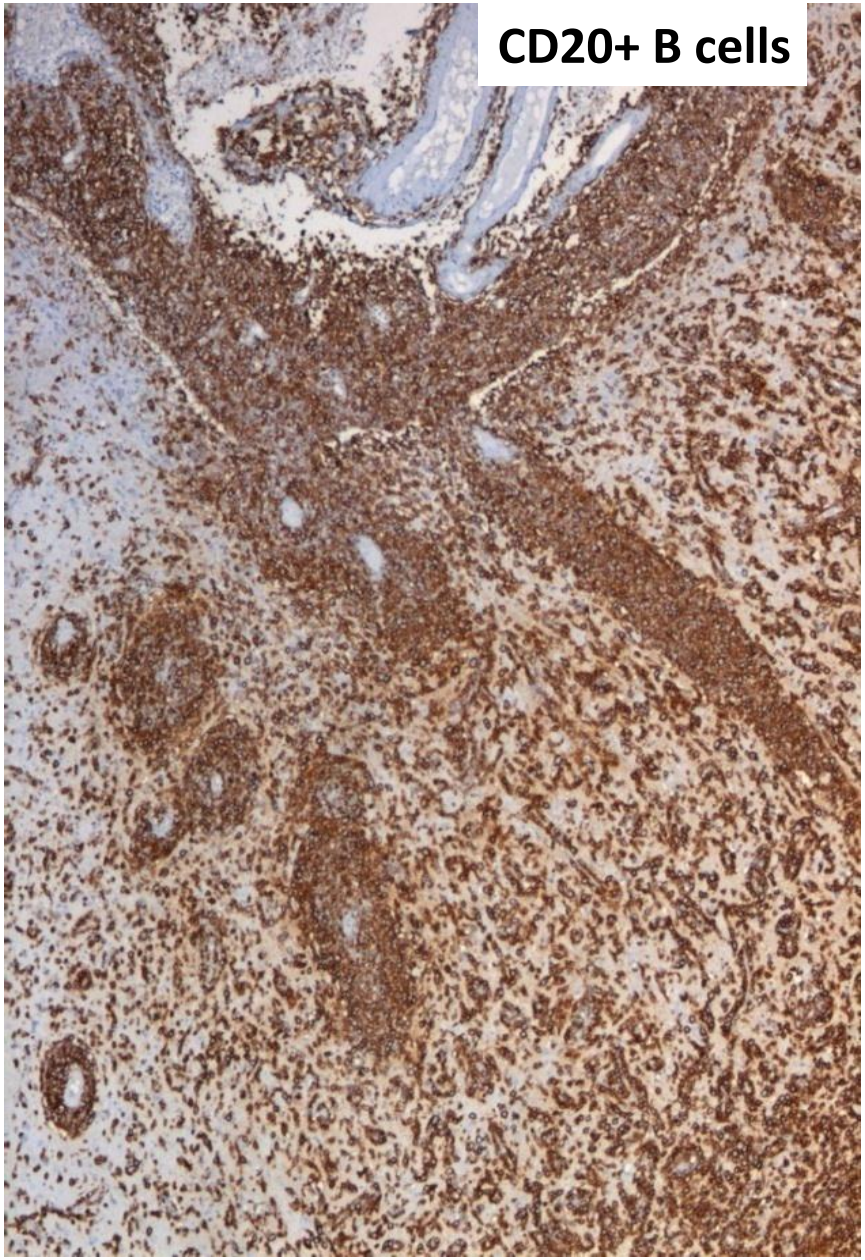
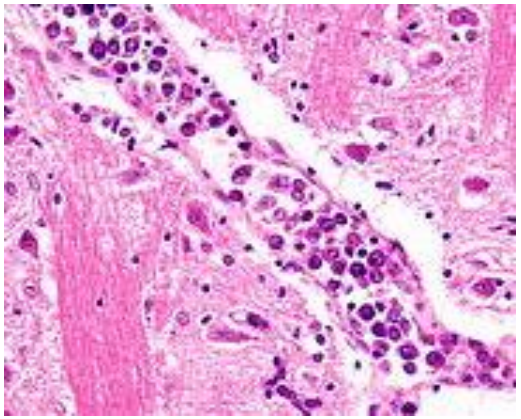

CD20+ B cells

Intravascular lymphoma

- Rare variant of DLBCL involving small and medium sized vessels producing occlusion , infarcts and hemorrhage
- The defining feature is



  - localization of neoplastic lymphoma cells within the vessel lumen
  - With minimal parenchymal extravasation.

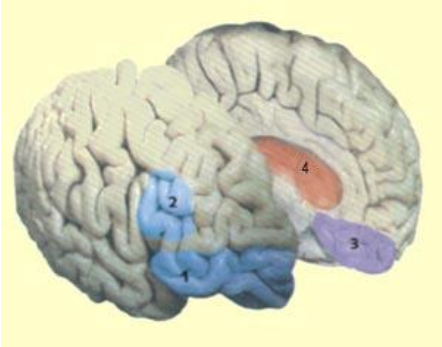
Q?... How often does PCNSL present as neurodegenerative disease?

- PCNSL commonly present with personality changes, irritability, memory loss, lethargy, confusion, disorientation, psychosis, dysphasia, ataxia, gait disorder, and myoclonus
- White-matter changes and CSF abnormalities predominate.
- Improved clinical awareness of PCNSL can prompt earlier diagnosis and treatment.

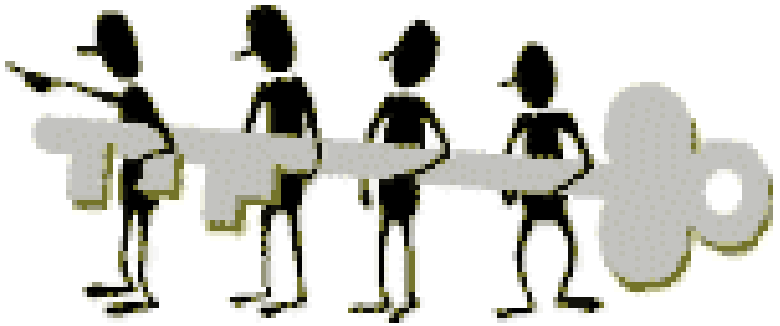
Was there a Role for autopsy in neuropsychiatric diseases??

Role of autopises?…

- Autopsies have aided in learning about mimcs
  - Infective
  - Immune mediated
  - Neoplastic causes



- But…advanced diagnostic tests (radiology, immunological tests…..)

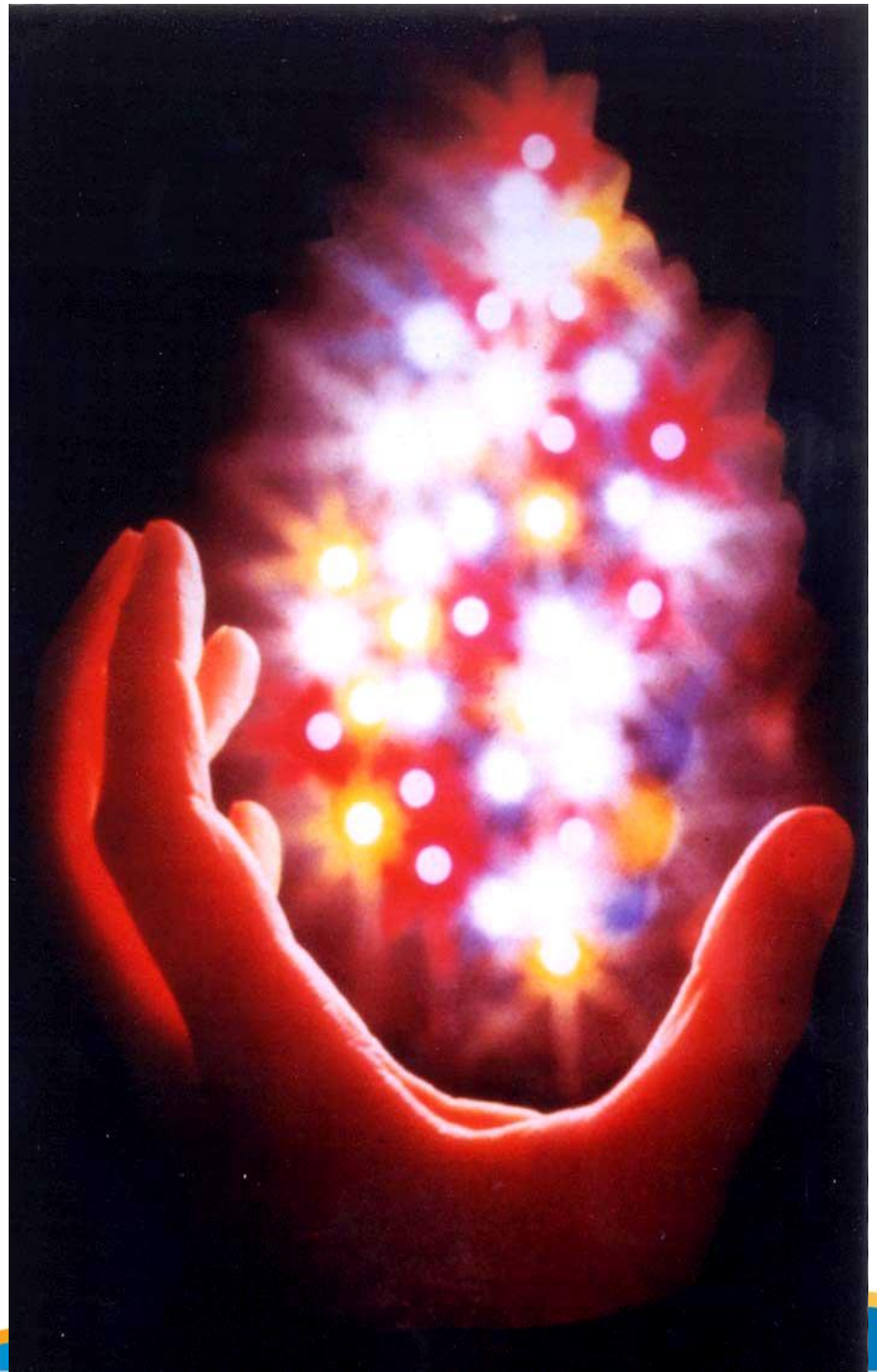


Take home…learning points

- Broaden the scope of tests to identify treatable/ potentially reversible causes.
- Serial imaging, contrast studies useful
- High index of suspicion, low threshold for biopsy
- Rely on your instinct! Its more often right than you think……

Is autopsy sill needed in this day and age?.....

MISSING LINK



Human Brain Tissue Repository (Brain Bank) 1995

NIMHANS, Bangalore

Only Brain Bank in the country

(Prof. SK Shankar)

Brain banking in Neuropsychiatric diseases….

- For the first time, it was demonstrated that major drug metabolizing enzymes Cytochrome P450 and flavin monooxygenases (FMO) were found in human brain tissues.
- Different isoforms of Cyt P450 was recognized in the human brain in alcoholics and epileptics treated with phenobarbitone.
- Dysfunction of serotonin (5HT) 2A receptors was found in psychiatric disorders like depression

Answers to few Qs….Brain Bank

- Infections and schizophrenia?
- **Multiplex PCR:** 5 DNA viruses (HSV, CMV, VZV, JCV, HHV-6), and T.gondii in CSF, serum and brain tissues (from autopsy) of 24 schizophrenia cases
  - CMV: 3 serum samples and one CSF sample,
  - HSV-2: CSF in one case
  - Toxoplasma gondii was detected in none

Role of autoimmunity in psychiatric disorders?... Brain Bank

- Schizophrenia: NMDA, AMPA, GABA, VGKC - CASPR, LGI – negative in 18 cases
- Cytokines: IL6 levels high and had unfavourable prognosis. sIL6R – auditory hallucinations
- OCD – anti basal ganglia antibodies (binding of CSF autoantibodies to homogenate of BG as well as to homogenate of thalamus among OCD patients)

S Bhattacharya, S Khanna, K Chakraborty, Mahadevan A, Shankar SK. Anti brain antibodies in obsessive compulsive disorder. Neuropsychopharmacology (2009) **34,** 2489–2496

“Omics…” in schizophrenia

- iTRAQ based quantitative proteomics and transcriptomics from anterior cingulate and dorsolateral prefrontal cortex, and hippocampus from cases of schizophrenia
- Key proteins differentially expressed
  - C-reactive protein, pentraxin-related (CRP), 2-oxoglutarate dehydrogenase, mitochondrial protein-OGDH (OGDH), mitochondrial creatine kinase, mitochondrial protein (CKMT2), porphobilinogen deaminase isoform 4 (HMBS), solute carrier family 15 (SLC 15A1), and S100 calcium binding protein A8 (S100A8).

- Physiological pathways
  - Peroxisome proliferator-activated receptors (PPAR) signaling pathway, Long-term depression, GABAergic synapse, Synaptic vesicle cycle, Retrograde endo cannabinoid signals, seretonerigc synapse, cholinergic synapse, calcium signaling pathway and oxidative phosphorylation.
- Several of the identified proteins have been known to play a role in neurodegenerative disorders - Alzheimer's and Parkinson's diseases
- ???Neurodegenerative disease????
- No animal models! Brain tissues…….

MISSING LINK

Dead men do tell tales…

Mruthyorma Amrutham Gamaya…..

Credits ....

- Psychiatry department, NIMHANS
- Dr. AB Taly, Dr.Madhu (Neurology, NIMHANS)
- Neuropathology, NIMHANS
- Thanks to....organisers (Dr. Suparna and Dr. Mehta) - Missing Links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