# Chronic meningitis and encephalitis

John Ferguson

UPNG 2013

jferguson@hnehealth.nsw.gov.au

# CHRONIC MENINGITIS

Two clinical forms of chronic meningitis :

1. symptoms are chronic and persistent

2. recurrent, discrete episodes of illness. All symptoms, signs, and CSF parameters of meningeal inflammation resolve completely between episodes without specific therapy.

# CSF examination

- Unexplained chronic headache, hydrocephalus, cranial neuropathy, radiculopathy, and/or cognitive decline should prompt CSF examination
- Significant meningitis can also be detected on CT or MRI but needs to be confirmed with CSF examination

**TABLE 361-1** *Symptoms and Signs of Chronic Meningitis*

| Symptom | Sign |
|---|---|
| Chronic headache | +/− Papilledema |
| Neck or back pain | Brudzinski's or Kernig's sign of meningeal irritation |
| Change in personality | Altered mental status—drowsiness, inattention, disorientation, memory loss, frontal release signs (grasp, suck, snout), perseveration |
| Facial weakness | Peripheral seventh CN palsy |
| Double vision | Palsy of CNs III, IV, VI |
| Visual loss | Papilledema, optic atrophy |
| Hearing loss | Eighth CN palsy |
| Arm or leg weakness | Myelopathy or radiculopathy |
| Numbness in arms or legs | Myelopathy or radiculopathy |
| Sphincter dysfunction | Myelopathy or radiculopathy<br>Frontal lobe dysfunction |
| Clumsiness | Ataxia |

***Note***: CN, cranial nerve.

# Chronic meningitis: key learning points

- The condition is most commonly diagnosed when a characteristic neurologic syndrome exists for > 4 weeks and is associated with a persistent inflammatory response in the cerebrospinal fluid (CSF) (white blood cell count >5/L).

- Five categories of disease account for most cases of chronic meningitis:
  1. meningeal infections: in PNG: **TB Meningitis, Cryptococcal meningitis and syphilis are the most important to know**
  2. malignancy
  3. non-infectious inflammatory disorders,
  4. chemical meningitis, and
  5. parameningeal infections

## TABLE 361-2 Infectious Causes of Chronic Meningitis

| Causative Agent | CSF Formula | Helpful Diagnostic Tests |
|---|---|---|
| **COMMON BACTERIAL CAUSES** | | |
| Partially treated suppurative meningitis | Mononuclear or mixed mononuclear-polymorphonuclear cells | CSF culture and Gram stain |
| Parameningeal infection | Mononuclear or mixed polymorphonuclear-mononuclear cells | Contrast-enhanced CT or MRI to detect parenchymal, subdural, epidural, or sinus infection |
| *Mycobacterium tuberculosis* | Mononuclear cells except polymorphonuclear cells in early infection (commonly <500 WBC/$\mu$L); low CSF glucose, high protein | Tuberculin skin test may be negative; AFB culture of CSF (sputum, urine, gastric contents if indicated); tuberculostearic acid detection in CSF; identify tubercle bacillus on acid-fast stain of CSF or protein pellicle; PCR |
| Syphilis (secondary, tertiary) *Treponema pallidum* | Mononuclear cells; elevated protein | CSF VDRL; serum VDRL (or RPR); fluorescent treponemal antibody-absorbed (FTA) or MHA-TP; serum VDRL may be negative in tertiary syphilis |
| **FUNGAL CAUSES** | | |
| *Cryptococcus neoformans* | Mononuclear cells; count not elevated in some patients with AIDS | India ink or fungal wet mount of CSF (budding yeast); blood and urine cultures; antigen detection in CSF |

**Always remember syphilis!!**

# Other infectious causes

| Causative Agent | CSF Formula | |
|---|---|---|
| **PROTOZOAL CAUSES** | | |
| *Toxoplasma gondii* | Mononuclear cells | + abscesses, HIV-associated |
| **HELMINTHIC CAUSES** | | |
| Cysticercosis (infection with cysts of *Taenia solium*) | Mononuclear cells; may have eosinophils; glucose level may be low | + abscesses |
| *Angiostrongylus cantonensis* | Eosinophils, mononuclear cells | 'Eosinophilic meningitis'; |
| **VIRAL CAUSES** | | |
| HIV (acute retroviral syndrome) | Mononuclear cells | At HIV seroconversion or in late AIDS |
| Herpes simplex (HSV) | Mononuclear cells | Recurrent meningitis associated with genital herpes recurrences |

# Non-infectious causes

- Malignancy: metastatic or primary
- Non-infectious inflammatory disorders: large range (SLE, Behcets, Wegeners granulomatosis,others); usually recurrent disease
- Chemical meningitis:
  - Drugs ibuprofen, sulfonamides, isoniazid, ciprofloxacin; improvement after discontinuation of drug; recurrent episodes with recurrent exposure

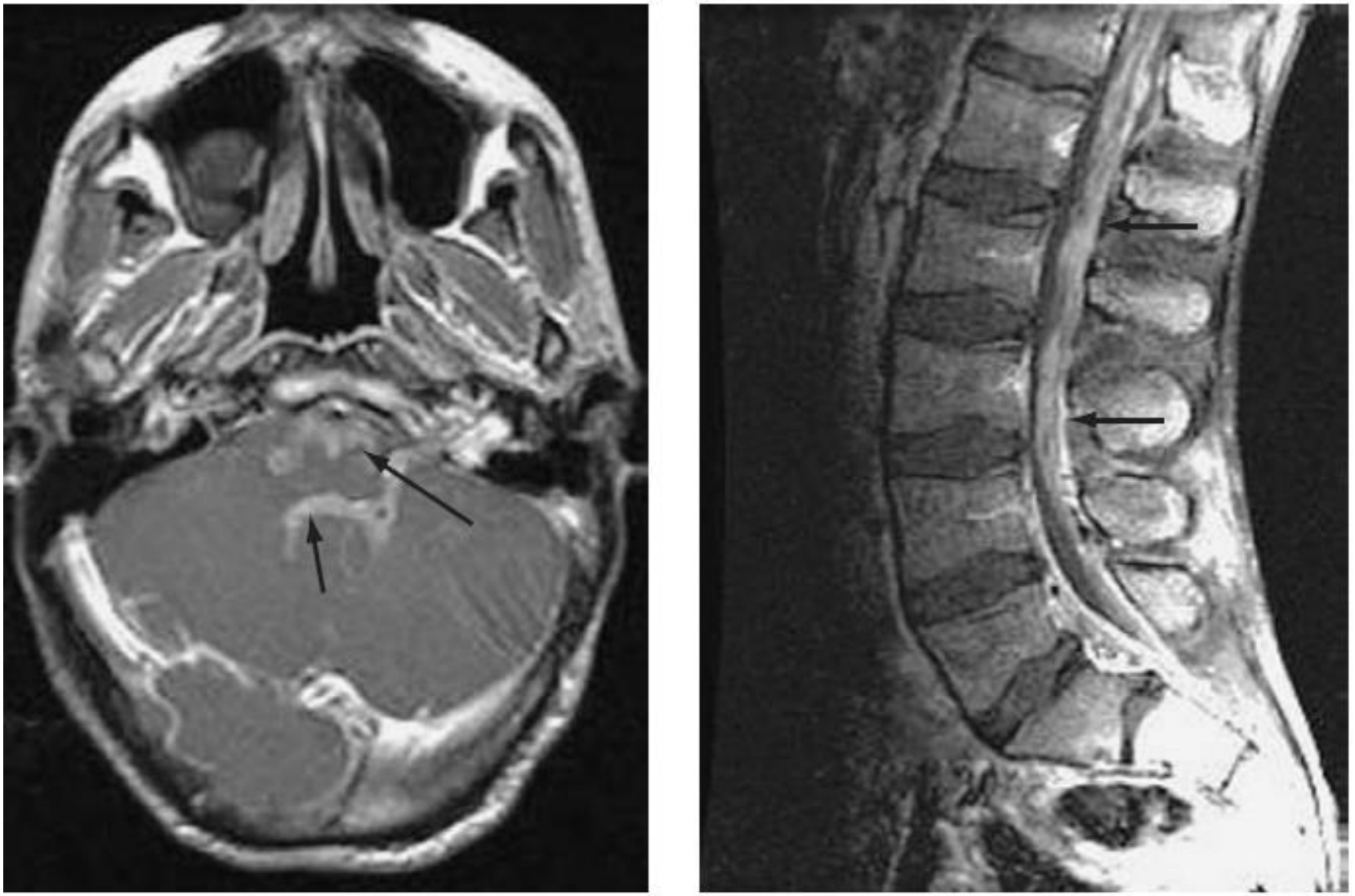


**FIGURE 361-1** Primary central nervous system lymphoma. A 24-year-old man, immunosuppressed due to intestinal lymphangiectasia, developed multiple cranial neuropathies. CSF findings consisted of 100 lymphocytes/$\mu$L and a protein of 250 mg/dL; cytology and cultures were negative. Gadolinium-enhanced T1 MRI revealed diffuse, multifocal meningeal enhancement surrounding the brainstem (*A*), spinal cord and cauda equina (*B*).

# *Cryptococcus neoformans*

- A dimorphic fungus that can cause disease in the apparently immunocompetent host without an underlying disease and those severely immunocompromised.
- Increasing cause of adult meningitis (subacute/chronic)
- Immunocompromised (HIV) hosts are particularly susceptible to *C. neoformans* whereas *C. gattii* often occur in immune competent individuals.

**Dimorphic** = exists as a yeast form at 35 deg. and a hyphal (filamentous) form at 25-30 degrees C

# *Cryptococcus neoformans*

Presentations:

- subacute meningitis: headache, fever, raised ICP
- pneumonia
- disseminated disease
- localised disease (cryptococcoma) - brain, lung

# Cryptococcosis

Diagnosis:

Microscopy (India Ink) and culture

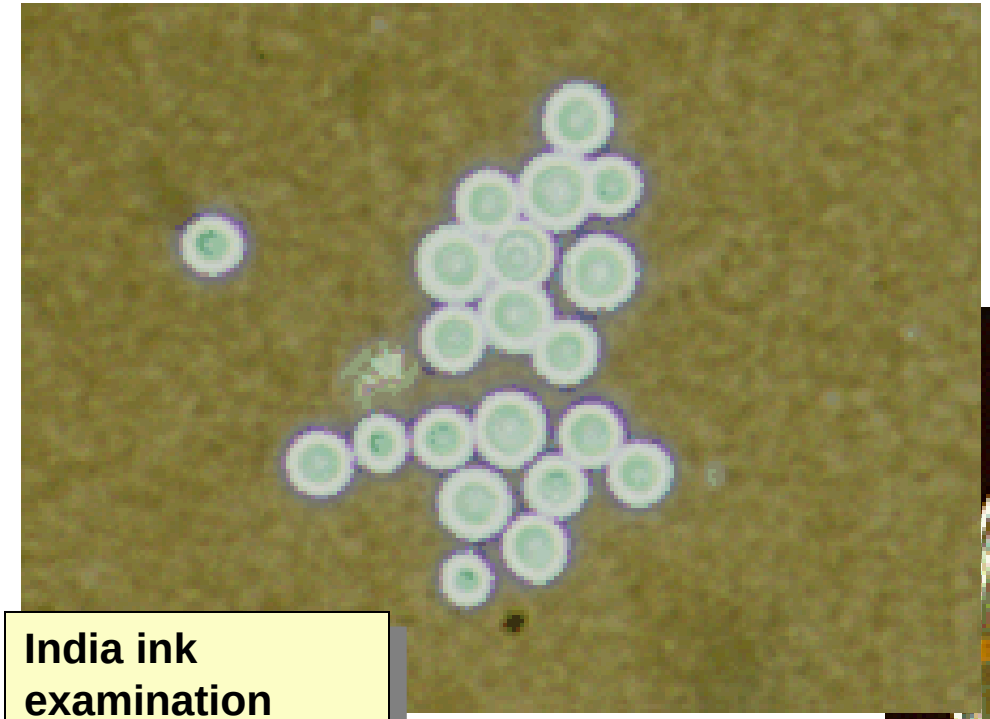
- CSF

- bronchial secretions or lung biopsy

Polysaccharide antigen detection is the best test:

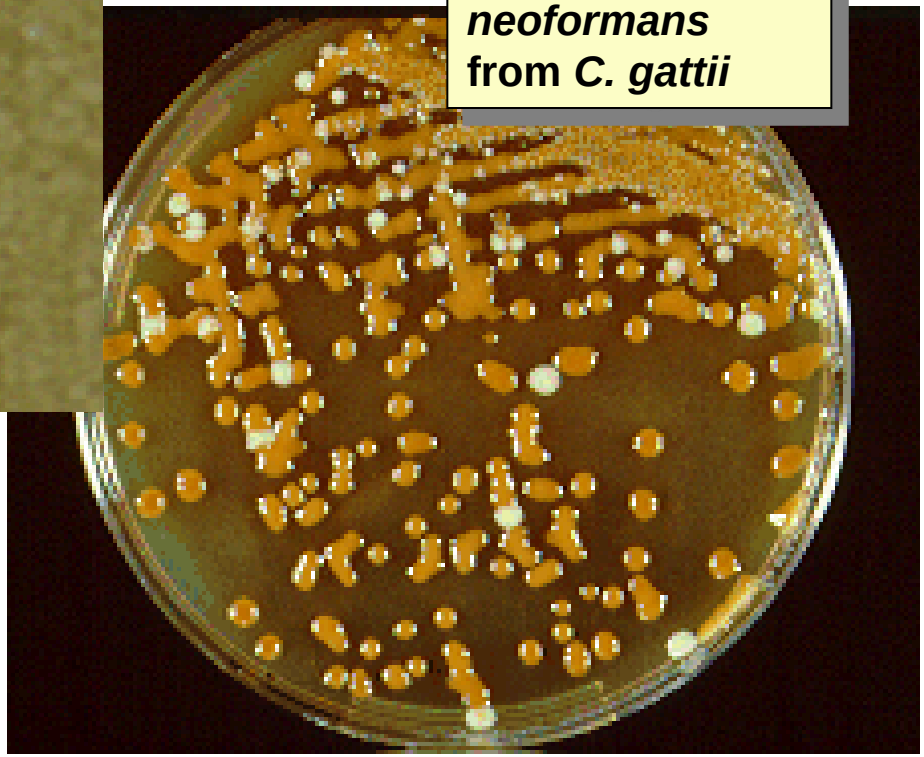
- serum or CSF latex agglutination

# *Cryptococcus neoformans*



**India ink examination**

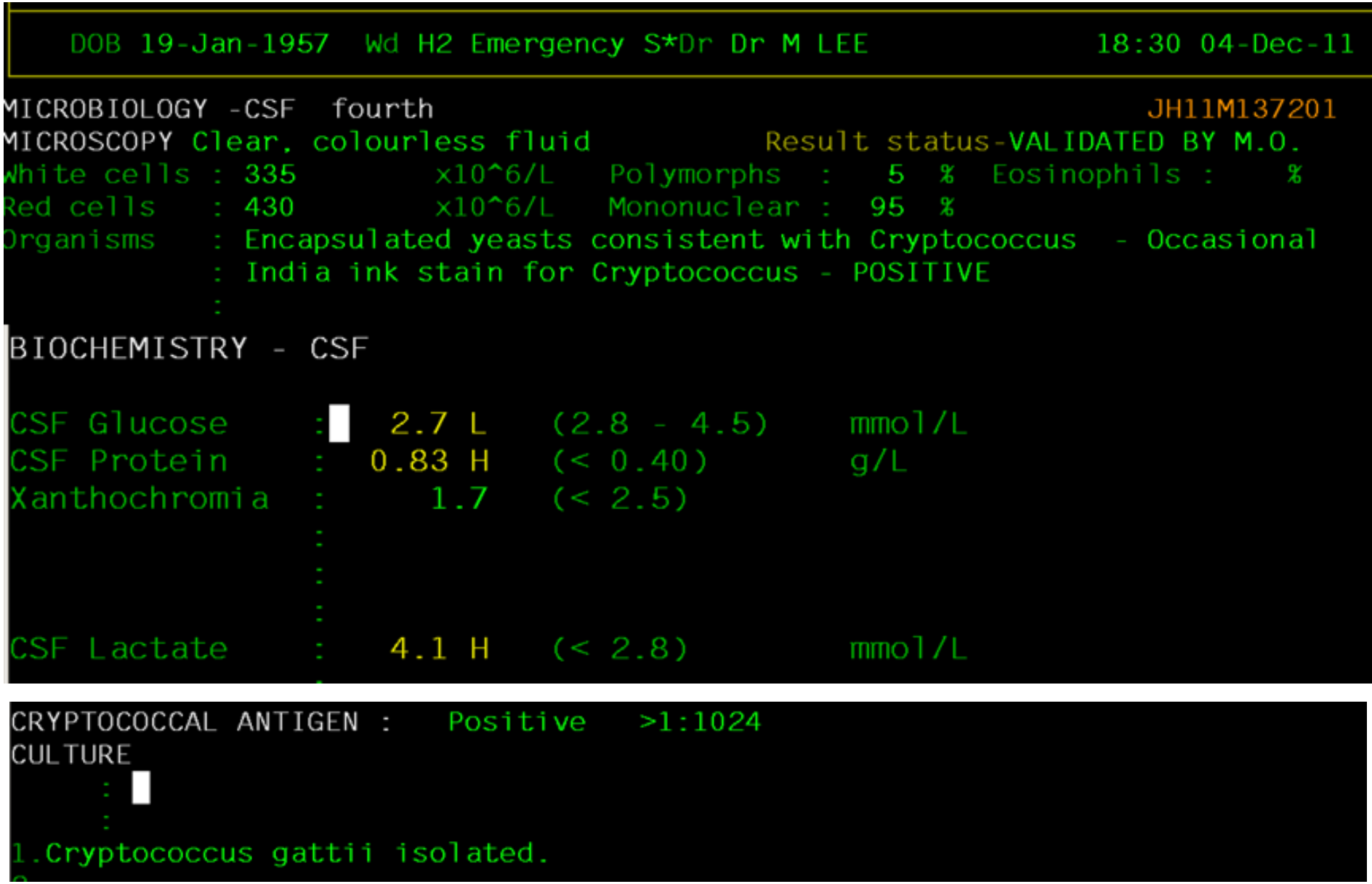
**Encapsulated yeast bodies of cryptococcus**



**Birdseed agar- used to distinguish *C. neoformans* from *C. gattii***

# Cryptococcal meningitis

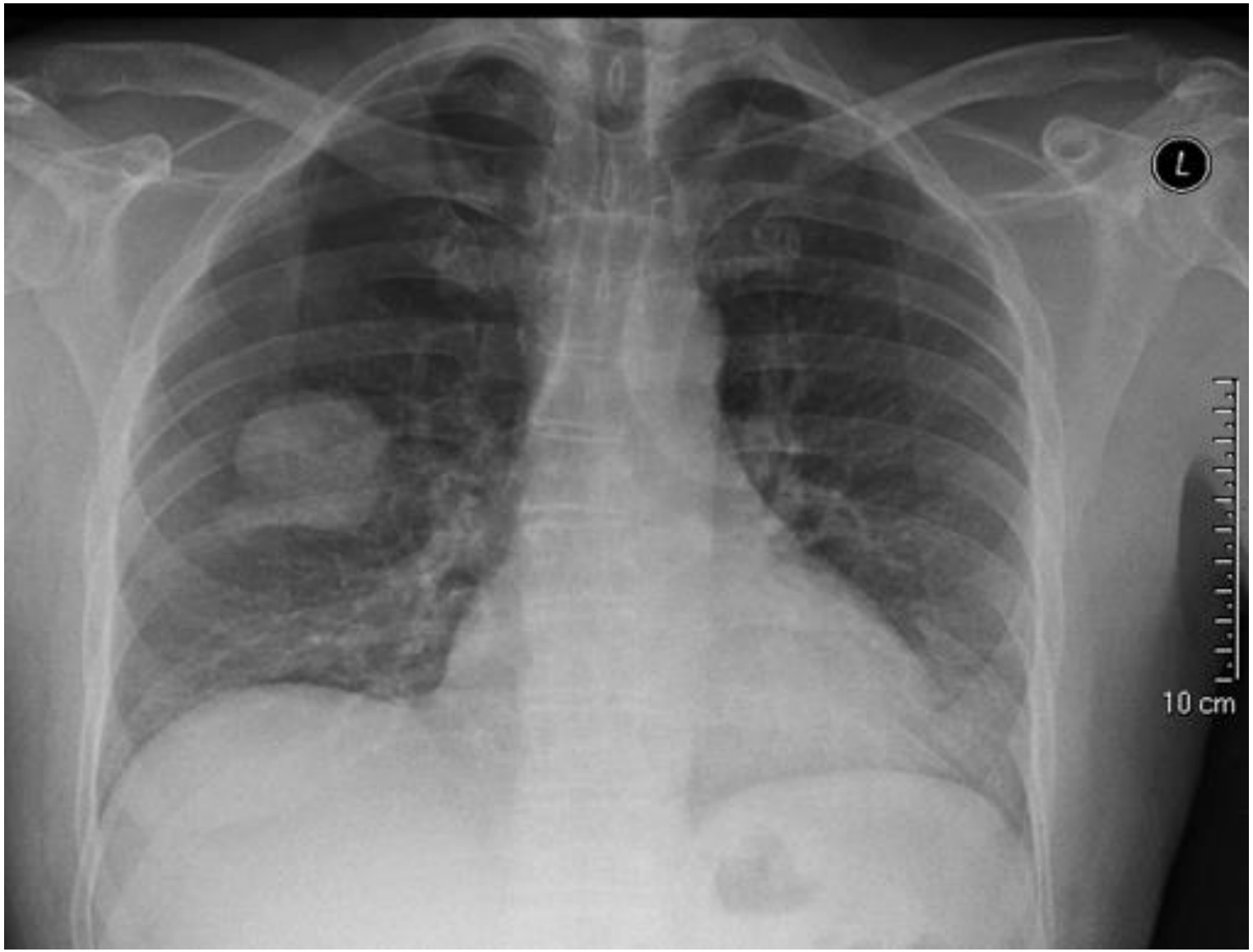
- Most patients with cryptococcosis of the CNS present with signs and symptoms of subacute meningitis or meningoencephalitis, such as headache, fever, cranial nerve palsies, lethargy, coma, or memory loss over several weeks.
- Symptoms may not be typical, and patients may present with acute (several days) symptoms of severe headaches, with intermittent headaches, or even with no headache but with altered mental status.



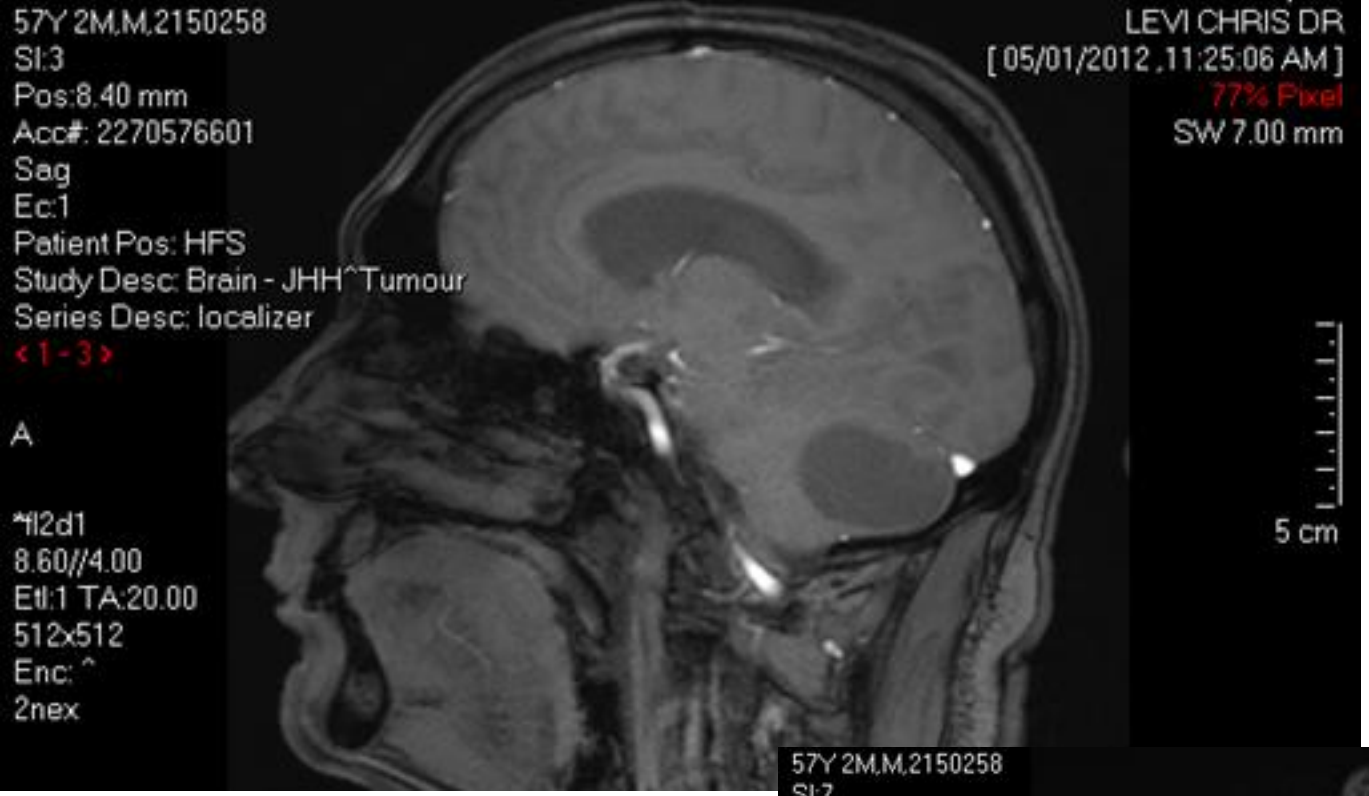
```
   DOB 19-Jan-1957  Wd H2 Emergency S*Dr Dr M LEE              18:30 04-Dec-11

MICROBIOLOGY -CSF  fourth                                        JH11M137201
MICROSCOPY Clear, colourless fluid          Result status-VALIDATED BY M.O.
White cells : 335        x10^6/L   Polymorphs  :   5  %  Eosinophils :    %
Red cells   : 430        x10^6/L   Mononuclear :  95  %
Organisms   : Encapsulated yeasts consistent with Cryptococcus  - Occasional
            : India ink stain for Cryptococcus - POSITIVE
            :

BIOCHEMISTRY - CSF

CSF Glucose     :  2.7 L    (2.8 - 4.5)     mmol/L
CSF Protein     : 0.83 H    (< 0.40)        g/L
Xanthochromia   :    1.7    (< 2.5)
                :
                :
                :
CSF Lactate     :  4.1 H    (< 2.8)         mmol/L
                :
```

```
CRYPTOCOCCAL ANTIGEN :   Positive   >1:1024
CULTURE
      :
      :
1.Cryptococcus gattii isolated.
```

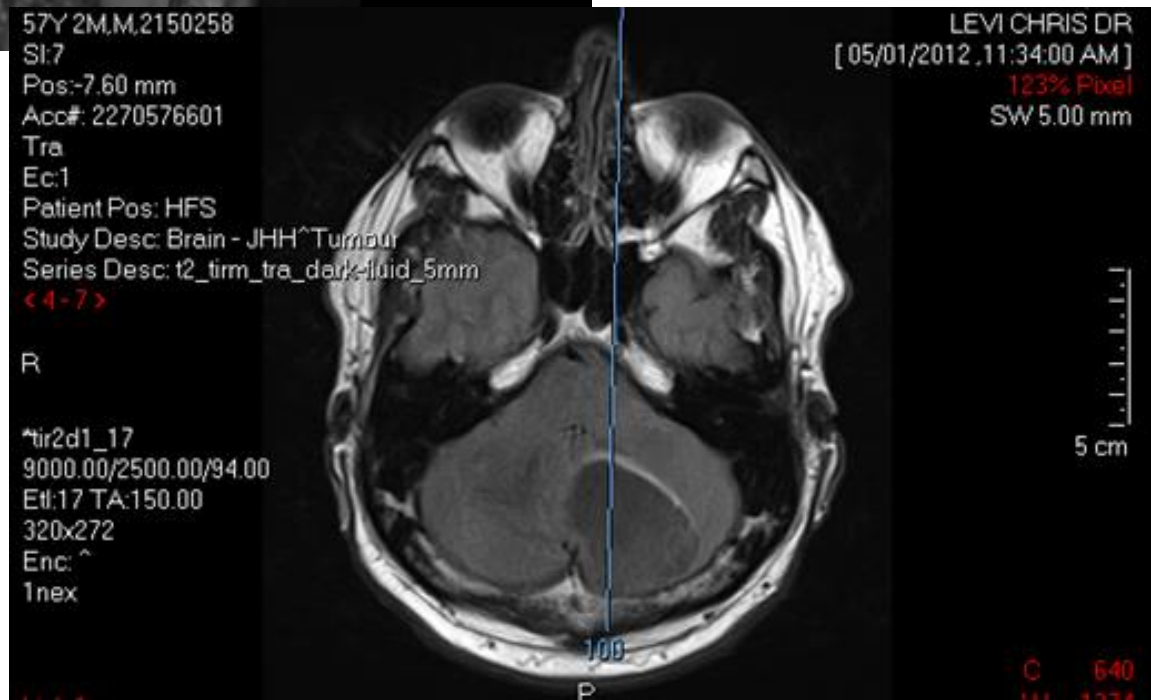
Arborist (tree surgeon) who presented with 4 wks of headaches. High CSF pressure treated with multiple LPs.




**Cryptococcoma in lung**




Recent *C. gattii* case with cerebellar abscess and lung lesion. Was mis-diagnosed as lung cancer with metastases to brain! A needle biopsy of the lung mass gave us the diagnosis.



# HIV-infected Patients

- The burden of yeast is generally higher, and this may be reflected slower conversion of CSF to culture negativity during treatment, and a tendency toward a higher incidence of increased intracranial pressure.
- Extracranial disease sites more likely to be found
- Important recent work that supports screening of new HIV patients for cryptococcus with blood antigen test at the time they start ARV treatment

Trop Doct. 2010 Jan;40(1):61-3.**Cryptococcal meningitis in immunocompetent Papua New Guinean children.**

We report three cases of meningo-encephalitis caused by *Cryptococcous gattii* in apparently immunocompetent children presenting to a provincial hospital in Papua New Guinea (PNG) over a nine-month period. After a postmortem diagnosis was made in the first case, a further two were identified quickly using Indian ink staining of cerebrospinal fluid (CSF). The second case had a complicated course and recovered after relapse. The third made a full recovery with appropriate antifungal therapy. Despite the fact that an environmental reservoir has not been established, cryptococcal meningo-encephalitis occurs regularly in PNG. In developing countries such as PNG, a lack of laboratory resources and limited therapeutic options can complicate the management of severe infections such as cryptococcosis. Nevertheless, with inexpensive diagnostic tests (such as Indian ink staining of CSF), a high index of suspicion and a pragmatic approach to antifungal therapy, good therapeutic outcomes can be achieved.

# Cost-Effectiveness of Serum Cryptococcal Antigen Screening to Prevent Deaths among HIV-Infected Persons with a CD4$^+$ Cell Count ⩽100 Cells/$\mu$L Who Start HIV Therapy in Resource-Limited Settings

SEE https://idmic.net/2016/04/02/saving-lives-by-routine-cryptococcal-antigen-screening-and-pre-emptive-fluconazole-in-patients-with-advanced-hiv/

**David B. Meya,[1,2,4] Yukari C. Manabe,[1,3] Barbara Castelnuovo,[1] Bethany , Andrew Kambugu,[1,4] Moses R. Kamya,[1,2] Paul R. Bohjanen,[4] and David F**

[1]Infectious Disease Institute, Makerere University, and [2]Makerere University College of Health Sciences, School of Medicine, Department of Medicine, Kampala, Uganda; [3]Johns Hopkins University School of Medicine, Baltimore, Maryland; and [4]Division of Infectious Disease and International Medicine, Department of Medicine, and Center for Infectious Disease and Microbiology Translational Research, University of Minnesota, Minneapolis, Minnesota

***Background.*** Cryptococcal meningitis (CM) remains a common AIDS-defining illness in Africa and Asia. Subclinical cryptococcal antigenemia is frequently unmasked with antiretroviral therapy (ART). We sought to define the cost-effectiveness of serum cryptococcal antigen (CRAG) screening to identify persons with subclinical cryptococcosis and the efficacy of preemptive fluconazole therapy.

***Methods.*** There were 609 ART-naive adults with AIDS who started ART in Kampala, Uganda, and who had a serum CRAG prospectively measured during 2004–2006. The number needed to test and treat with a positive CRAG was assessed for ⩾30-month outcomes.

***Results.*** In the overall cohort, 50 persons (8.2%) were serum CRAG positive when starting ART. Of 295 people with a CD4$^+$ cell count ⩽100 cells/$\mu$L and without prior CM, 26 (8.8%; 95% confidence interval [CI], 5.8%–12.6%) were CRAG positive, of whom 21 were promptly treated with fluconazole (200–400 mg) for 2–4 weeks. Clinical CM developed in 3 fluconazole-treated persons, and 30-month survival was 71% (95% CI, 48%–89%). In the 5 CRAG-positive persons with a CD4$^+$ cell count ⩽100 cells/$\mu$L treated with ART but not fluconazole, all died within 2 months of ART initiation. The number needed to test and treat with CRAG screening and fluconazole to prevent 1 CM case is 11.3 (95% CI, 7.9–17.1) at costs of $190 (95% CI, $132–$287). The number needed to test and treat to save 1 life is 15.9 (95% CI, 11.1–24.0) at costs of $266 (95% CI, $185–$402). The cost per disability-adjusted life year saved is $21 (95% CI, $15–$32).

Clinical Infectious Diseases 2010

# Cryptococcus: learning points

1. Presentation and diagnosis
2. Treatment to sterilise CSF: induction and maintenance; culture CSF after 2 wks of treatment to check – should be no growth
3. Treatment to aggressively manage raised intracranial pressure: improves outcomes, reduces visual complications
4. Primary and secondary prophylaxis with fluconazole for HIV patients with low CD4 count (<250)

# TB meningitis: pathogenesis

- Miliary tubercles form in the parenchyma of the brain during hematogenous dissemination of tubercle bacilli in the course of primary infection.
- These tubercles enlarge and are usually caseating. The propensity for a caseous lesion to produce meningitis is determined by its proximity to the subarachnoid space and the rate at which fibrous encapsulation develops.
- Caseous foci cause meningitis via discharge of bacilli and tuberculous antigens into the subarachnoid space.
- Mycobacterial antigens produce intense inflammatory reaction in the CSF - thick exudate formed that surrounds the cranial nerves and major blood vessels at the base of the brain.

# TB meningitis : presentation

- Subacute : unrelenting headache, neck stiffness, fatigue, night sweats, eventually altered level of consiousness/coma
- The classic CSF abnormalities (NB. atypical findings may occur):
  - elevated opening pressure,
  - Lymphocytic pleocytosis (10 to 500 cells/L),
  - elevated protein concentration in the range of 1 to 5 g/L
  - Decreased glucose concentration (moderate)
- CSF AFB examination 10-40% sensitive and culture 50 % sensitive and slow! PCR more sensitive

# TBM: learning points

- Presentation and diagnosis: must suspect early
- Early presumptive treatment: delay associated with poor outcomes
- Combination tuberculous chemotherapy with addition of corticosteroids
- Active management of raised intracranial pressure – repeated LPs, CSF shunt sometimes

# ENCEPHALITIS

- Cerebral inflammation often with meningism
- Focal or generalised process
- **Telltale indicators- impaired level of consciousness, seizures, fever**

**PNG considerations-**

Cerebral MALARIA and TB must always be considered!

Herpes simplex encephalitis – treatable if diagnosed early

SSPE (post measles encephalitis)

Dengue

Japanese encephalitis

[Kuru! (prion disease)- no new diagnoses now]

# CNS Case 4:

13 year old girl  presented with one day history of headache, neck stiffness, nausea and collapse. During the collapse, she was unresponsive and was noted to be stiff on the left side with facial twitching , right-sided eye deviation followed by a left-sided Todd's paresis.

- Admitted to ICU. Brain CT scan was normal. Temperature 38°C.
- Given aciclovir for 2 days. Fever settled; home soon after.
- Provisional diagnosis: 'migraine' (family history).
- Given aspirin for treatment.

***Questions:***

*What would your differential diagnosis of this problem have been?*

# CNS case 4: Differential diagnosis

- The history is of an acute febrile neurological disorder with evidence of focal seizure activity and some meningism.  An infective process should be top most in mind.  The normal CT scan  largely rules out a focal process such as brain abscess.
- The clinical picture suggests meningo-encephalitis. Herpes simplex encephalitis must be considered strongly.

# CNS case 4:progress

Readmission 9 days after original admission after a tonic/clonic seizure with right-sided paresis and eyes deviated to left.

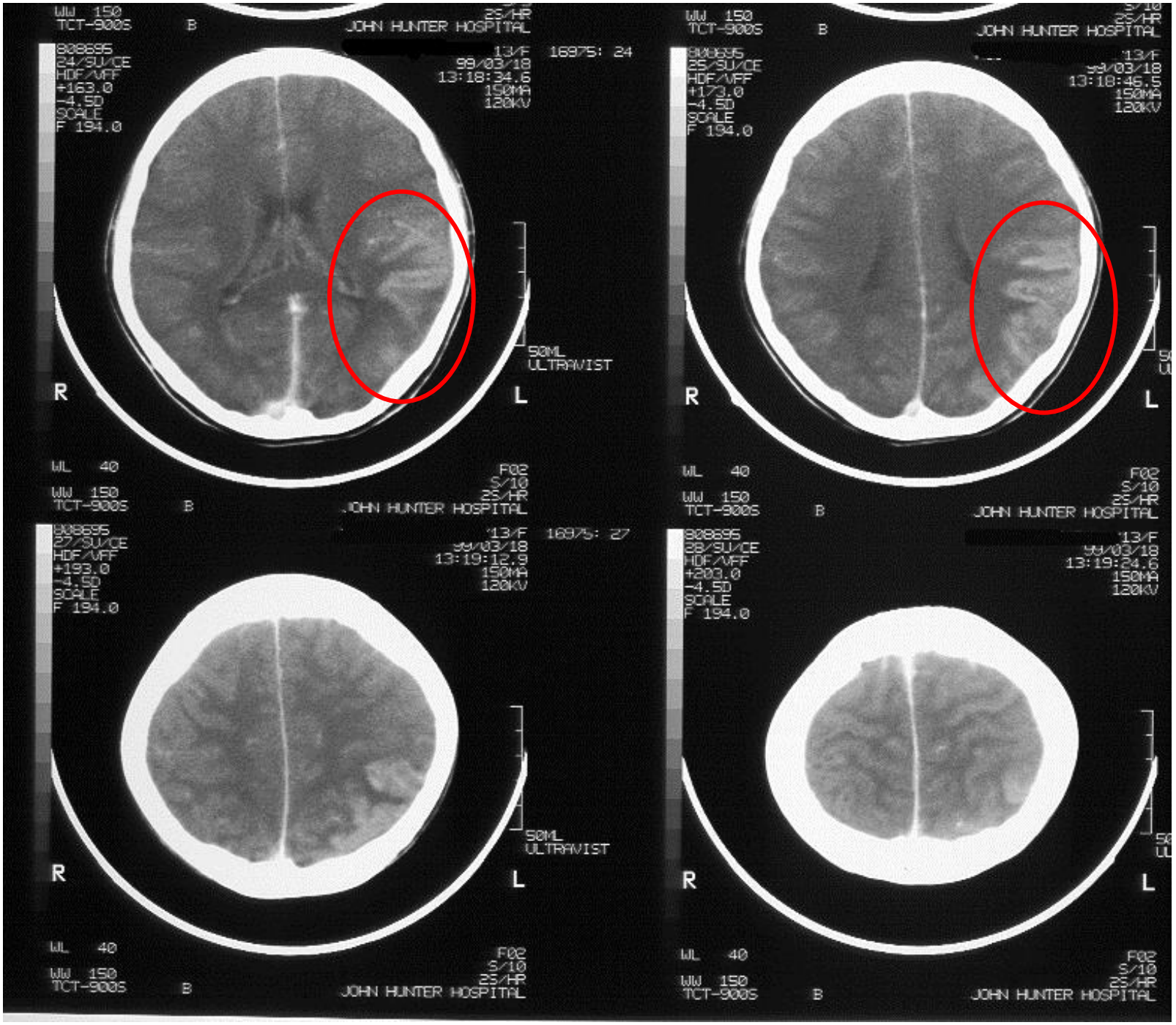
WCC: 14.0, Hb and platelets normal

CSF : cells 16 x 10^6/L WC (85% monos), 1 x 10^6/L RBC

| | |
|---|---|
| glucose | 2.9 mmol/L |
| protein | 0.18 g/L (normal <0.4g/L) |
| xanthochromia | < 0.5 |

Electro-encephalogram report (EEG):

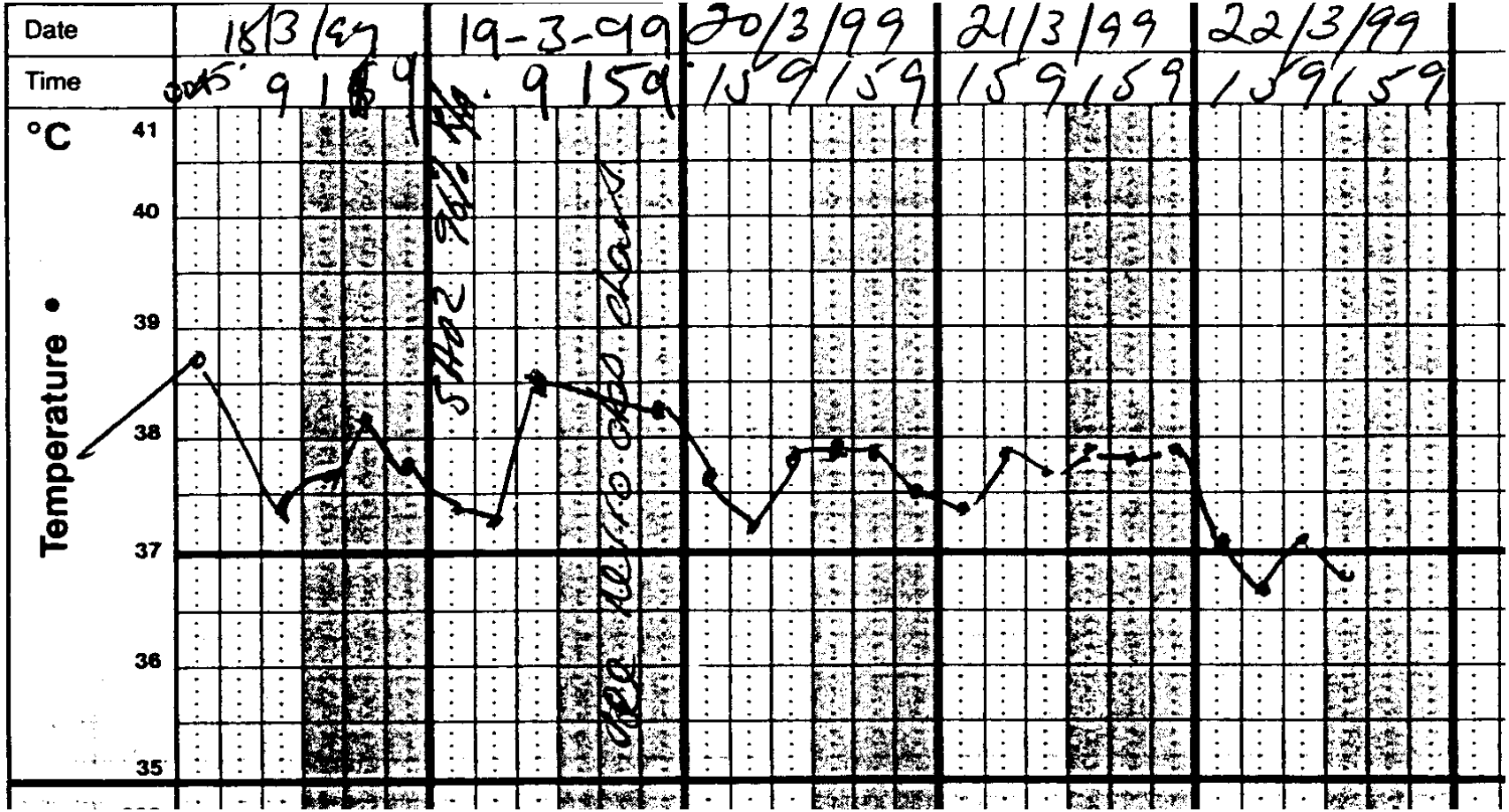
Conclusion: Markedly abnormal record with prominant focal slowing generally over the left hemisphere along with focal epileptiform discharges from the left central region. The features are in keeping with a focal inflammatory or ischaemic process in the left hemisphere.


WW 150
TCT-900S
B
JOHN HUNTER HOSPITAL
808695
24/SU/CE
HDF/VFF
+163.0
-4.5D
SCALE
F 194.0
13/F 16875: 24
99/03/18
13:18:34.6
150MA
120KV
50ML
ULTRAVIST
R
L
WL 40
WW 150
TCT-900S
B
F02
S/10
25/HR
JOHN HUNTER HOSPITAL
808695
25/SU/CE
HDF/VFF
+173.0
-4.5D
SCALE
F 194.0
13/F
99/03/18
13:18:46.5
150MA
120KV
R
L
WL 40
WW 150
TCT-900S
B
F02
S/10
25/HR
JOHN HUNTER HOSPITAL
808695
27/SU/CE
HDF/VFF
+193.0
-4.5D
SCALE
F 194.0
13/F 16875: 27
99/03/18
13:19:12.9
150MA
120KV
50ML
ULTRAVIST
R
L
WL 40
WW 150
TCT-900S
B
F02
S/10
25/HR
JOHN HUNTER HOSPITAL
808695
28/SU/CE
HDF/VFF
+203.0
-4.5D
SCALE
F 194.0
13/F
99/03/18
13:19:24.6
150MA
120KV
R
L
WL 40
WW 150
TCT-900S
B
F02
S/10
25/HR
JOHN HUNTER HOSPITAL

# CNS Case 4- Diagnosis and management

- The CT scan findings were compatible with either a left fronto-parietal infarct or cerebritis.
- The findings of CSF pleocytosis, focal EEG and CT abnormalities are **strongly suggestive of herpes simplex encephalitis.**
- Early treatment with high dose intravenous aciclovir continued for 14 days at least whenever the diagnosis is suspected.
- The patient received a full course of aciclovir and progressed well (see temperature chart). She was given phenytoin and had no further seizures.
- Herpes simplex PCR on CSFwas positive, confirming the diagnosis.

# Case 4- response to treatment



# Differential diagnosis of encephalitis

- Infective causes (next slide)
- Meningitis (PNG: TB, or Cryptococcus)
- Parameningeal focus
- Causes of encephalopathy-
  - Systemic infections, severe sepsis
  - metabolic disturbances (hypoglycaemia, hyponatraemia and hypocalcaemia);
  - thiamine deficiency (Wernicke's encephalopathy);
  - drugs (including neuroleptics [neuroleptic malignant syndrome], trimethoprim–sulfamethoxazole, isoniazid, nonsteroidal anti-inflammatory drugs, intoxications); and
  - Various auto-immune inflammatory disorders
- Status epilepticus and malignancy (paraneoplastic syndrome) may also sometimes be confused with encephalitis.

## 9: Clinical clues as to cause of encephalitis

*Herpes simplex virus:* Temporal lobe signs often prominent (personality change, hallucinations)

*Varicella–zoster virus:* Cerebellar ataxia (children), progressive confusion (adults)

*Epstein–Barr virus:* Meningoencephalitis (immunocompromised)

*Human herpesvirus 6:* Focal encephalitis (immunocompromised adults)

*Murray Valley encephalitis virus:* Involvement of thalamus, brain-stem, cerebellum and spinal cord

*Japanese encephalitis virus:* Brainstem involvement, meningeal signs may be striking, parkinsonian signs (40% overall mortality)

*Cytomegalovirus:* Insidiously progressive (similar to AIDS dementia)

*Enteroviruses:* May occur in epidemics, chronic course in patients with hypogammaglobulinaemia (enterovirus type 71 causes epi-demic meningoencephalitis; brainstem involvement prominent)

*Poliovirus:* Involvement of spinal cord and brainstem

*Rabies virus:* Hyperaesthesia at inoculation site

*Burkholderia pseudomallei (melioidosis):* Brainstem involvement

*Listeria monocytogenes:* Occurs at extremes of age, brainstem involvement

**PNG:**

SSPE (over)

Herpes simplex

Japanese EV

Murray valley encephalitis

Enterovirus

*Listeria*

[? melioidosis

[? Rickettsia

**SUBACUTE SCLEROSING PANENCEPHALITIS** SSPE is a rare progressive demyelinating disease of the CNS associated with a chronic infection of brain tissue with measles virus. Most patients give a history of primary measles infection at an early age (2 years), which is followed after a latent interval of 6 to 8 years by the development of insidious intellectual decline and mood and personality changes. Typical signs of a CNS viral infection, including fever and headache, do not occur. Focal and/or generalized seizures, myoclonus, ataxia, and visual disturbances occur as the disease progresses. The EEG shows a characteristic periodic pattern with bursts every 3 to 8 s of high-voltage, sharp slow waves, followed by periods of attenuated ("flat") background.

Epidemiol Infect. 2003 Oct;131(2):887-98.

**A continuing high incidence of subacute sclerosing panencephalitis (SSPE) in the Eastern Highlands of Papua New Guinea.**

From February 1997 to April 1999 we diagnosed a total of 55 patients with SSPE at Goroka Base General Hospital in Eastern Highlands Province (EHP) of PNG. The diagnosis was based on high cerebrospinal fluid and serum measles virus antibody titres with progressive neurological disorder and myoclonic jerks.

Of these 55 patients 42 were from EHP, including 32 whose onset was in the 2-year period 1997-1998. **The annual incidence of SSPE in EHP in these 2 years was 98 per million population under 20 years of age, the highest ever reported.** This incidence was more than ten times higher than the highest incidence in the prevaccine era reported from elsewhere.

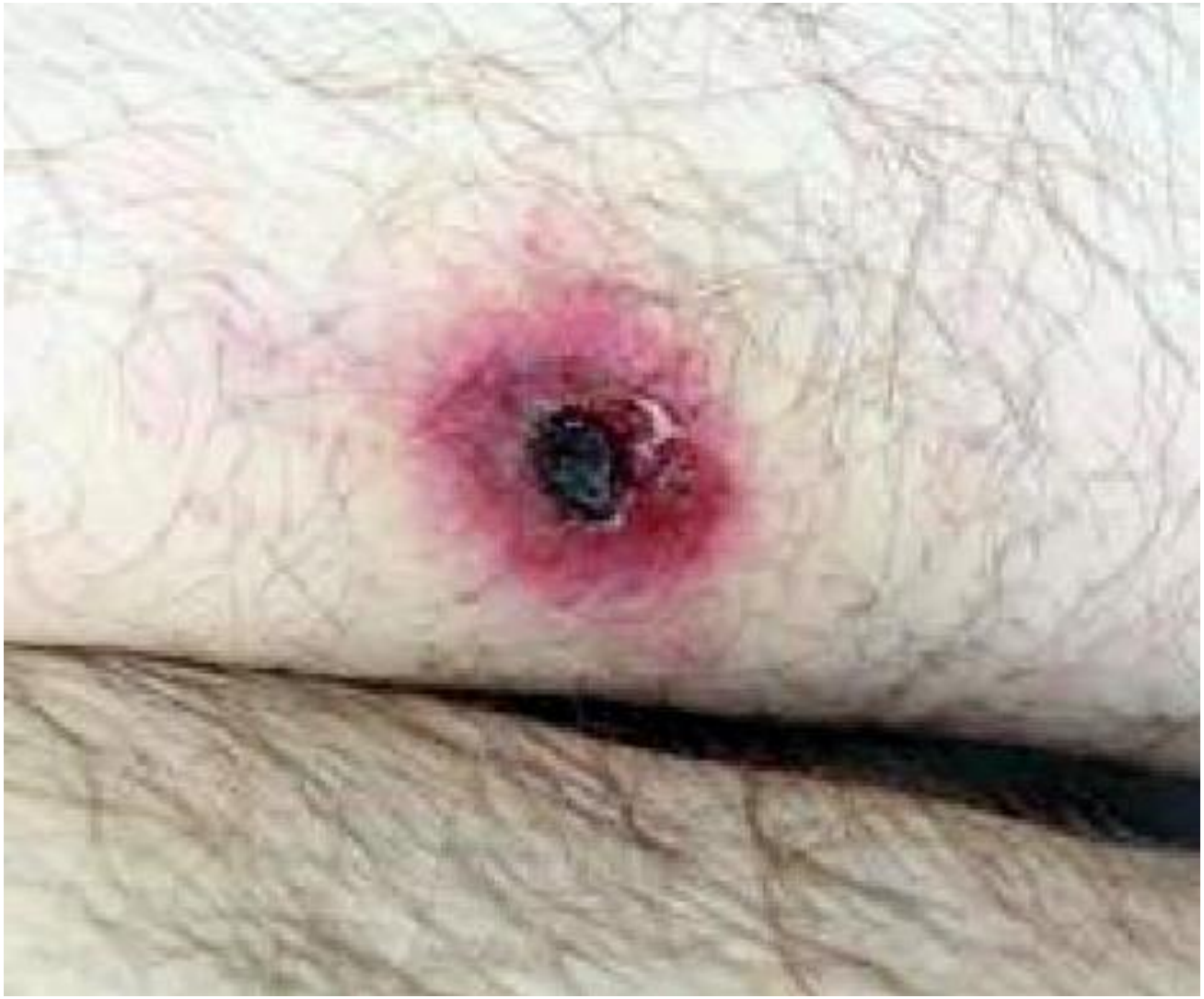
The mean age of onset of SSPE was 7.7 years (range 2.8-14.8 years) and the interval between measles and the onset of SSPE, where known, had a mean of 5.9 years and a range of 2.5-11.1 years. We found no evidence to implicate measles vaccination in the development of SSPE.

# Rickettsial diseases and scrub typhus

- Febrile illness which may be severe and associated with headache and photophobia
- Spotted fever (*R. australis*) – patient develops widespread spotty rash (petechiae) which is non-blanching (ie. haemorrhagic). Tick borne.
- Scrub typhus *(Orientia tsutsugamushi)*: often no rash but black spot (tache noire ) is common- site of the mite bite. Illness quite severe.
- Encephalitis is uncommon with these diseases- mostly they do not involve the central nervous system
- Low platelet count and blood leucopenia usually occur

- The extent of these diseases in PNG needs to be defined with further study!

# “Tache noire” = Black spot



P N G Med J. 2007 Sep-Dec;50(3-4):172-83.

# Scrub typhus (*Orientia tsutsugamushi),* spotted fever (Rickettsia australis) and dengue fever as possible causes of mysterious deaths in the Strickland Gorge area of Southern Highlands and West Sepik Provinces of Papua New Guinea.

Spicer PE, Taufa T, Benjamin AL.

A medical investigation was carried out in April 2001 into an outbreak of a mysterious haemorrhagic disease and deaths in the remote Strickland River area of Papua New Guinea (PNG). 9 villages were visited and 140 persons, consisting of immediate blood relatives of the deceased (cases) and others in the village picked at random (controls), were physically examined. Specimens of blood, urine and faeces were collected from each person for laboratory tests in PNG and Australia.

Positive sera for dengue (15%) and Japanese encephalitis (JE) (6%) were identified. Surprisingly, **a number of the sera were positive for scrub typhus (Orientia tsutsugamushi)** (28%) and spotted fever (Rickettsia australis) (11%). The last reported cases of scrub typhus in PNG were during World War Two among the allied troops. **This is the first time spotted fever (R. australis) has been reported in PNG.** These conditions may have been the cause of the deaths described by the villagers. However, there were significantly more dengue-positive results among relatives of the deceased than non-relatives though no such difference was found with rickettsial infections: **haemorrhagic dengue fever is thus the most likely cause of this recurring outbreak.**

# Encephalitis: key learning

- Presentation and diagnosis
- Herpes simplex encephalitis
- PNG : what is the infectious differential diagnosis (many unknowns!!)
- Other non-infectious causes of encephalopathy