Abnormal CSF F.I.

When too many tests are barely enough

Andrew Mahony

Austin Health

1st March 2011

The patient

- 51yo male
- Arrived in Melbourne from UK 2 days prior
- Brought to ED by concerned sister
  - “He’s just not himself since we last saw him”
  - Snoring 18 months, ?apnoeas
  - Lethargic 6 months, sleeping during day
  - Weight gain ?30kg over 3 months
  - Forgetting his lines 6 weeks
  - Personality change, loss of libido
  - Intermittent double vision and slurred speech over weeks

Past history

- Low testosterone Dx recently by GP in UK
- Myocardial infarct 10yrs ago
- Hyperlipidaemia

Medications
Aspirin
Atorvastatin
Herbal medicine (snoring)

- Non-smoker
- ~3 glasses wine / night
- Father lung Ca, mother pancreatic Ca

Social history

- Wife, 5 children
- No other sexual partners
- No illicit drug use
- 2 pet kittens, 1 dog
- Large garden, compost

- No known TB contacts

Travel history

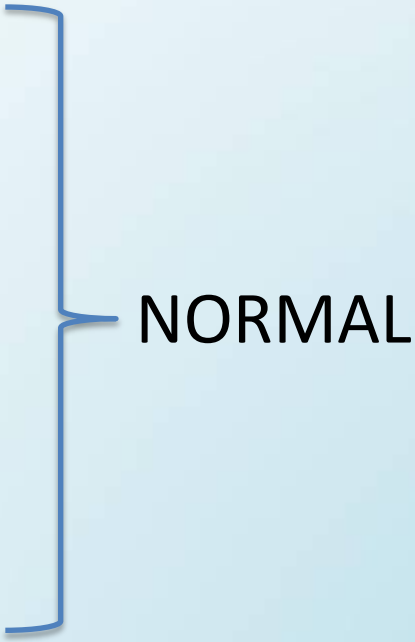
- Born in Melbourne
- Lives near London
- Brisbane October – December 2010
- Sydney late 2009
- Boston 2009
- Denver 2005
- Continental Europe

Examination findings

- Well, sitting in chair reading – fell asleep
- No fever
- No photophobia / neck stiffness
- Ophthalmoparesis
  - Downward gaze palsy
  - L eye restricted abduction
- No other neurological signs

Initial work-up

- FBE
- ESR
- UEC
- Ca, Mg, PO4
- CRP
- LDH
- TSH
- LFT
  - ALT 64 U/L(<45)
  - GGT 119 U/L (<55)



Imaging

- CXR
- CT Brain
- U/S Liver

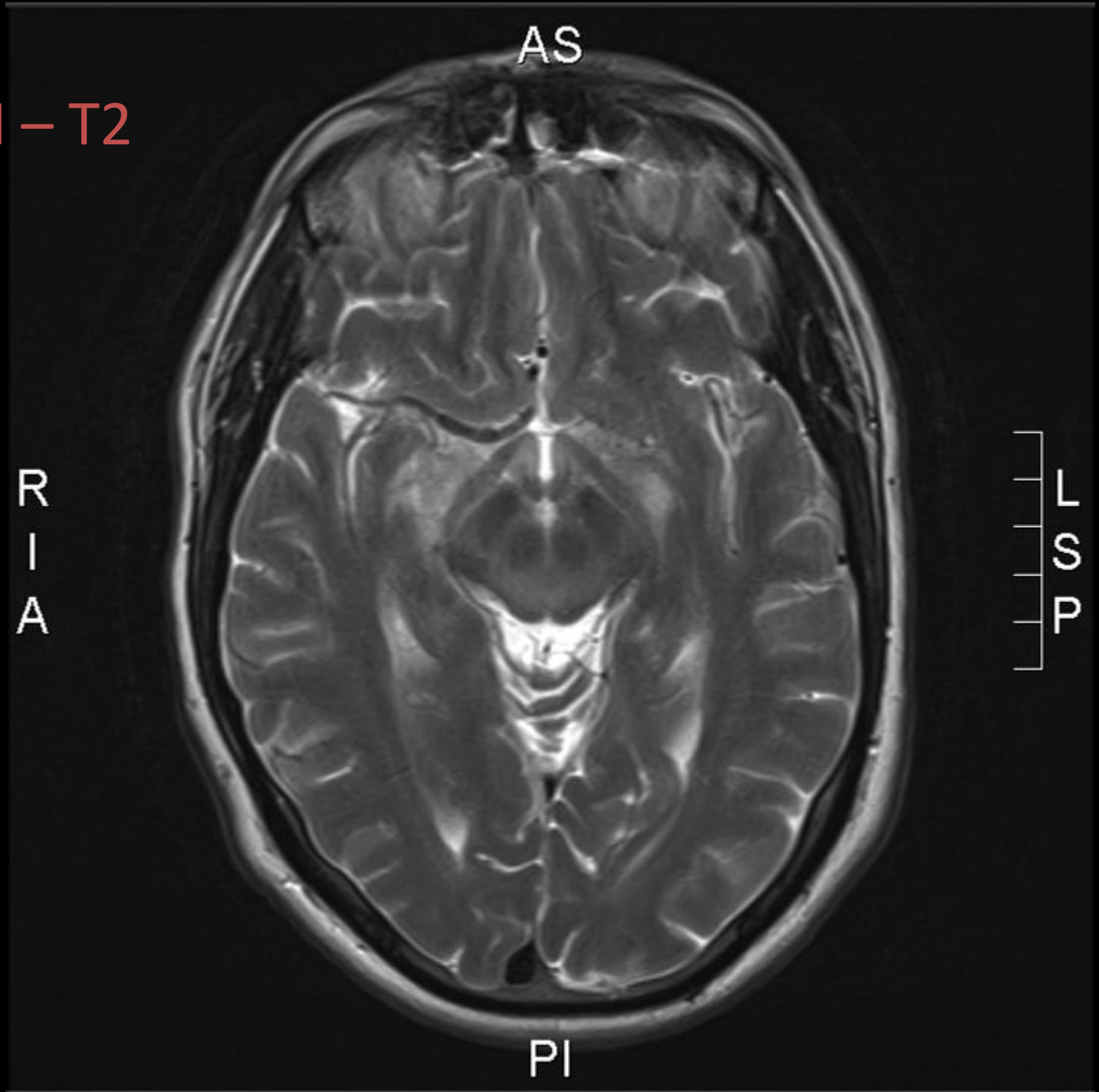
NORMAL

EEG also normal

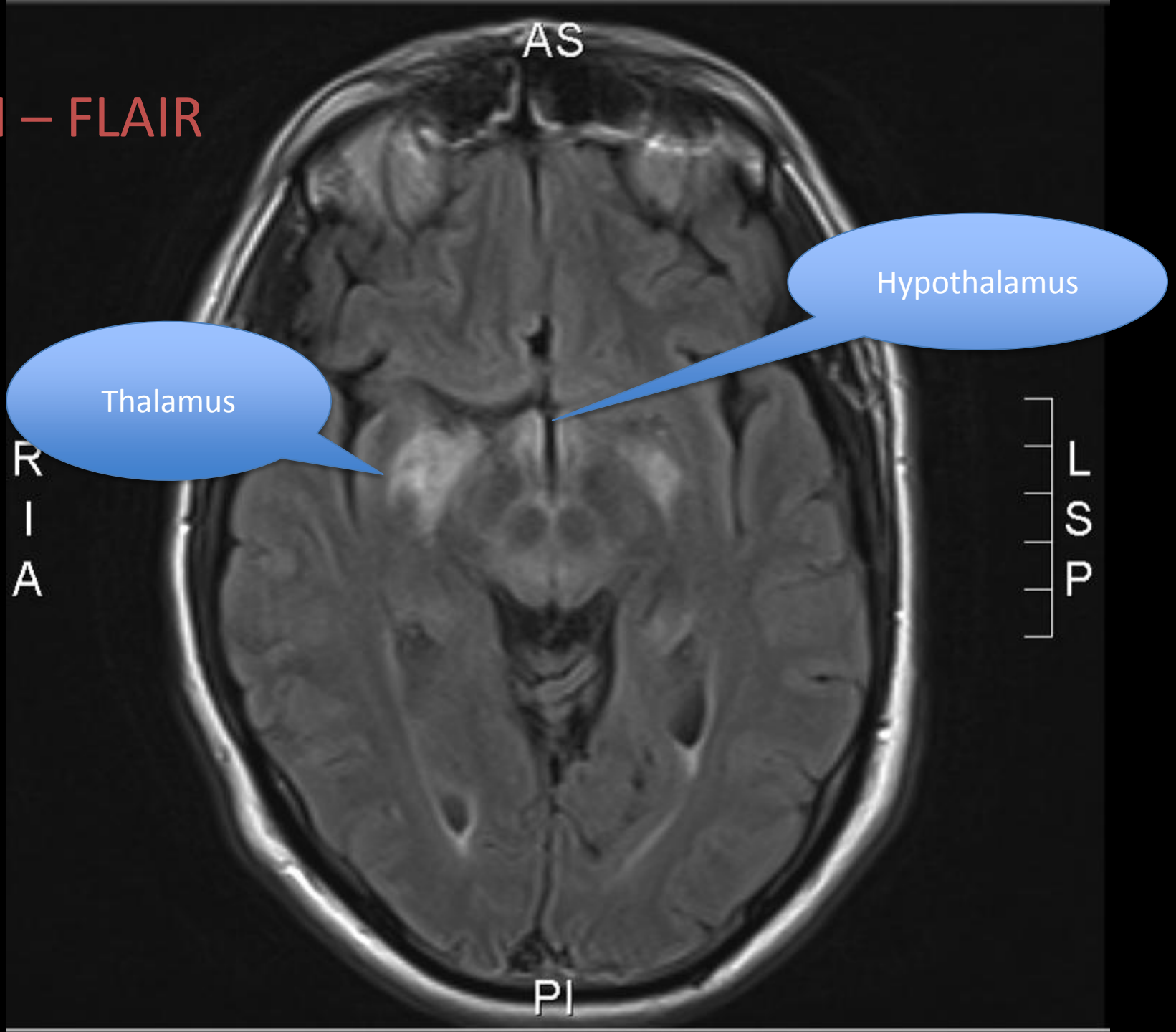
CSF

Time	Day 2
Protein (g/L)	1.03
Glucose (mmol/L)	3.9
White cell count (x10^6/L)	7 monos, 0 polys
Red cell count (x10^6/L)	2
Cytology	Lymphocytosis
Protein electrophoresis	No oligoclonal bands
What about now?	

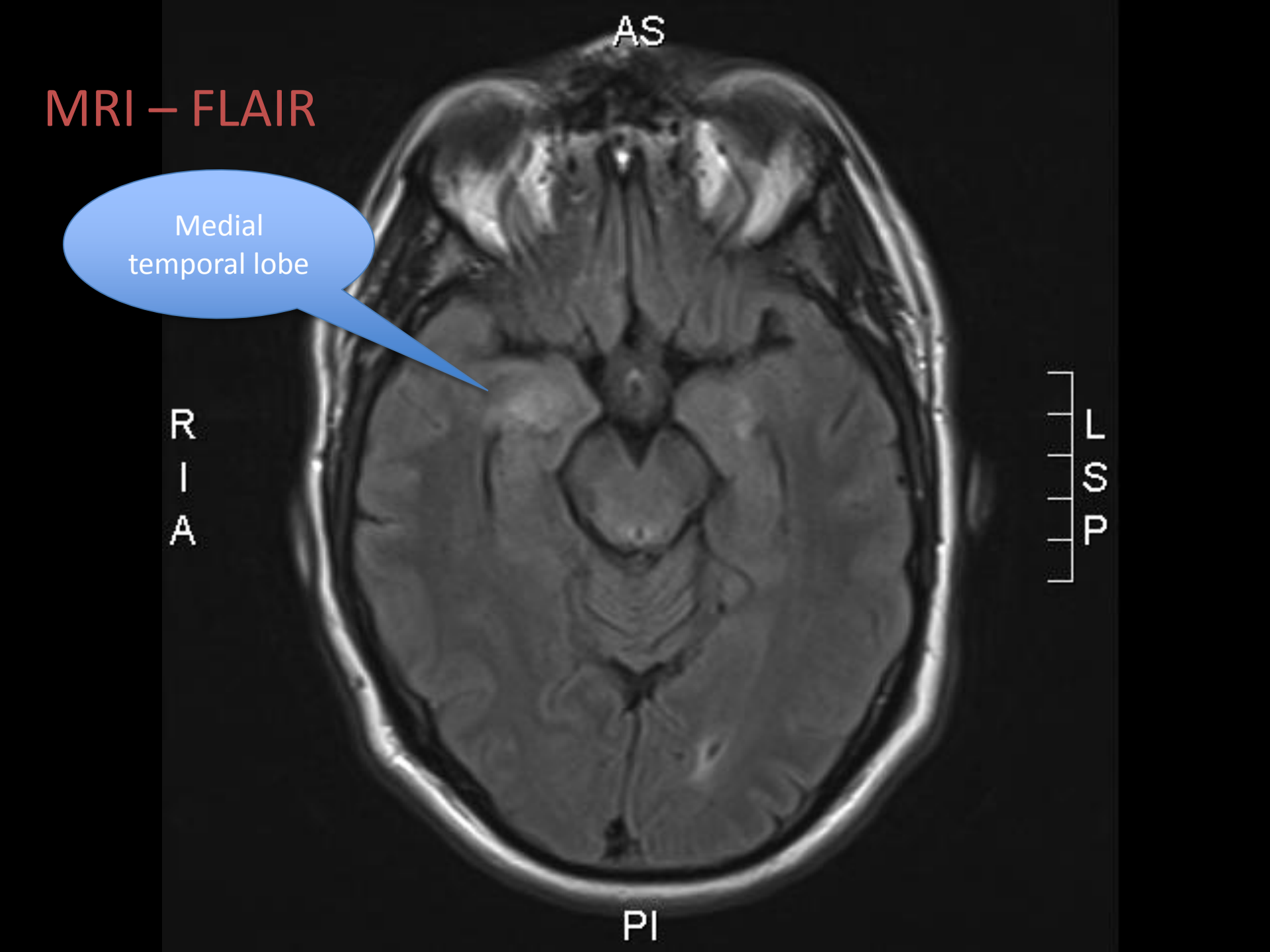
MRI – T2



MRI – FLAIR



MRI – FLAIR



Clinical equipoise: ID vs Neurology

- ID DDx:
  - Non-infectious
  - Atypical HSV
  - Whipple's
  - HIV + OI
  - Syphilis
  - Bartonella
  - ?TB, others
- "We would like some more CSF please"

- Neurology DDx:
  - Autoimmune encephalitis of limbic + extralimbic systems
- "Does he have cancer?"
- "How much steroid should we start?"

Further CSFs

Time	Day 2	Day 6	Day 31	Day 52
Protein (g/L)	1.03	0.78	1.28	1.30
Glucose (mmol/L)	3.9	4.6	9.3	4.6
White cell count ($x10^6$/L)	7 monos	5 monos	1 mono	2 monos
Red cell count ($x10^6$/L)	2	2	0	4
Cytology	Lymphocy sis	Lymphocytosis	Monocytosis	Normal
Protein electrophoresis	No oligo nal bands		Flow cytometry – T cells	
Volume for culture	1.5mL	10mL	6mL	8mL
Culture	GPB P.	Negative TB negativ	Negative	Negative

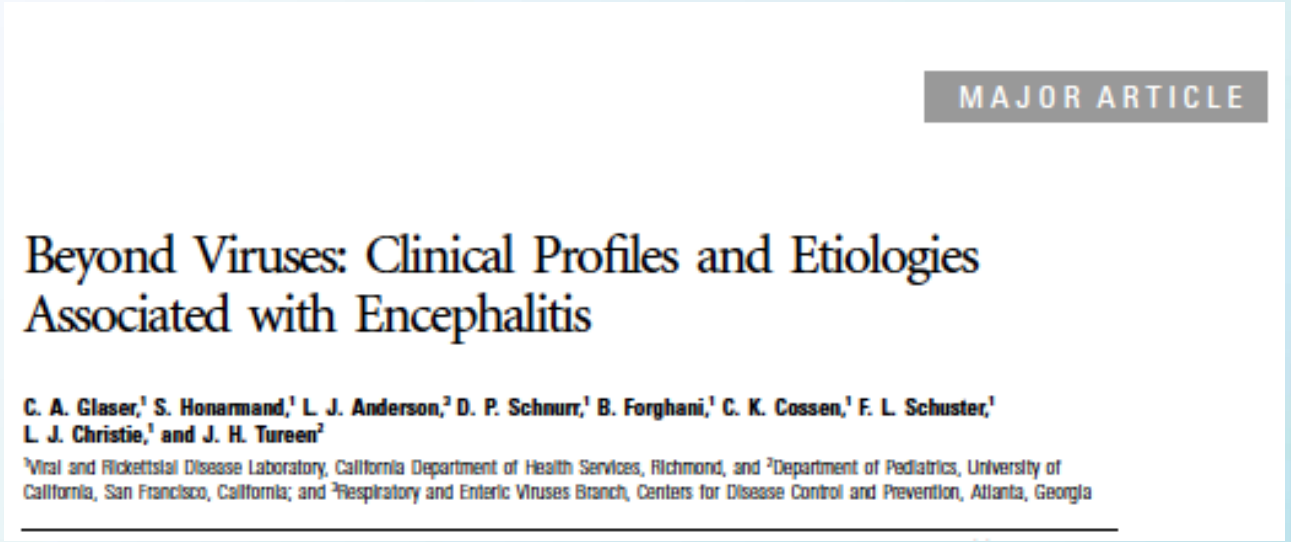
2nd relapse
IVIg x3
Pred 75mg

IVIg daily x5

Relapse
Pulse methyl pred
Further IVIg x3
Home on pred 60mg

“Systematic utilisation” of California Encephalitis Project protocol…

- Serology
  - Syphilis
  - HIV
  - HBV
  - HCV
  - Toxoplasma
  - Bartonella
  - Mycoplasma
  - Legionella
  - Borrelia
  - Cryptococcus (serum, CSF Ag)
- Quantiferon Gold in-tube
- IgG positive, IgM negative
  - CMV
  - EBV
  - Measles
  - HSV-1, HSV-2
  - VZV
  - Rubella
  - Mumps
- CSF PCRs
  - Herpes multiplex (HSV, VZV, CMV)
  - EBV
  - HHV-6
  - Tropheryma whipplei
  - Flavivirus (JE, MVE, Kunjin)
  - Measles
  - TB


MAJOR ARTICLE

Beyond Viruses: Clinical Profiles and Etiologies Associated with Encephalitis

C. A. Glaser,[1] S. Honarmand,[1] L. J. Anderson,[2] D. P. Schnurr,[1] B. Forghani,[1] C. K. Cossen,[1] F. L. Schuster,[1] L. J. Christie,[1] and J. H. Tureen[2]

[1]Viral and Rickettsial Disease Laboratory, California Department of Health Services, Richmond, and [2]Department of Pediatrics, University of California, San Francisco, California; and [3]Respiratory and Enteric Viruses Branch, Centers for Disease Control and Prevention, Atlanta, Georgia

(CID 2006)

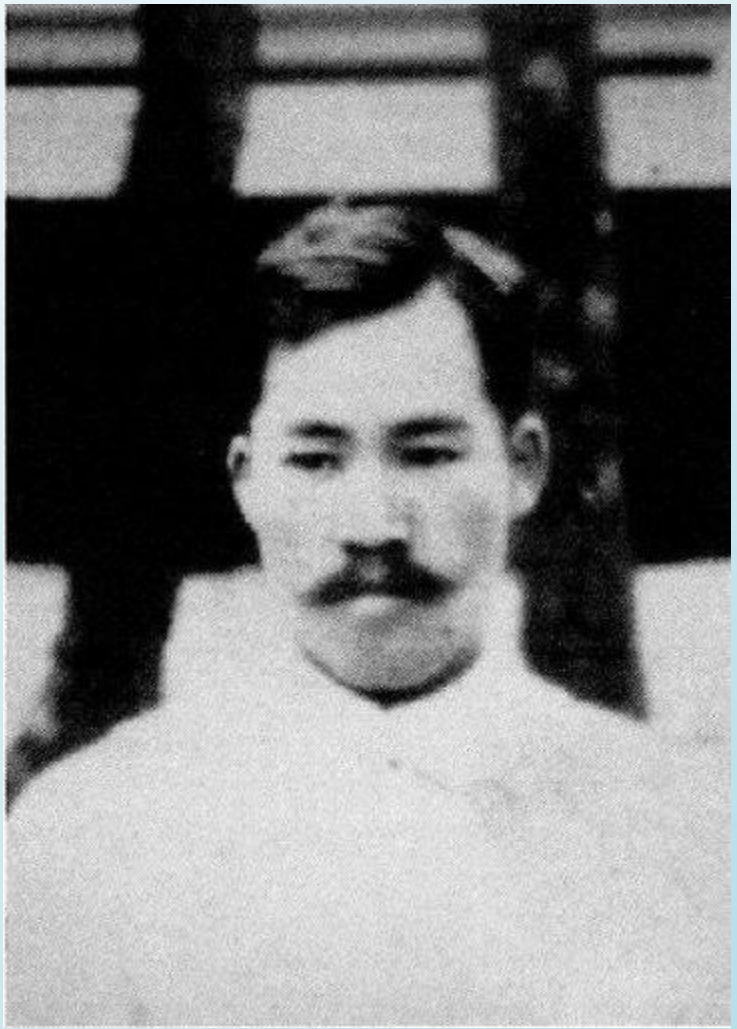
Autoimmune Ix

- ANA
- ANCA
- dsDNA
- ENA
- C3, C4
- Rheumatoid factor, anti-CCP, cryoglobulins
- ACE
- Anti-neuronal antibodies
  - Hu, Yo, Ri, Tr, Ma, CV2
  - GQ1b
- Anti-thyroid antibodies
  - Peroxidase 282 IU/mL (<5.61)
  - Thyroglobulin 12 IU/mL (<4.11)

Autoimmune encephalitis
with
Obstructive +/- central sleep apnoea

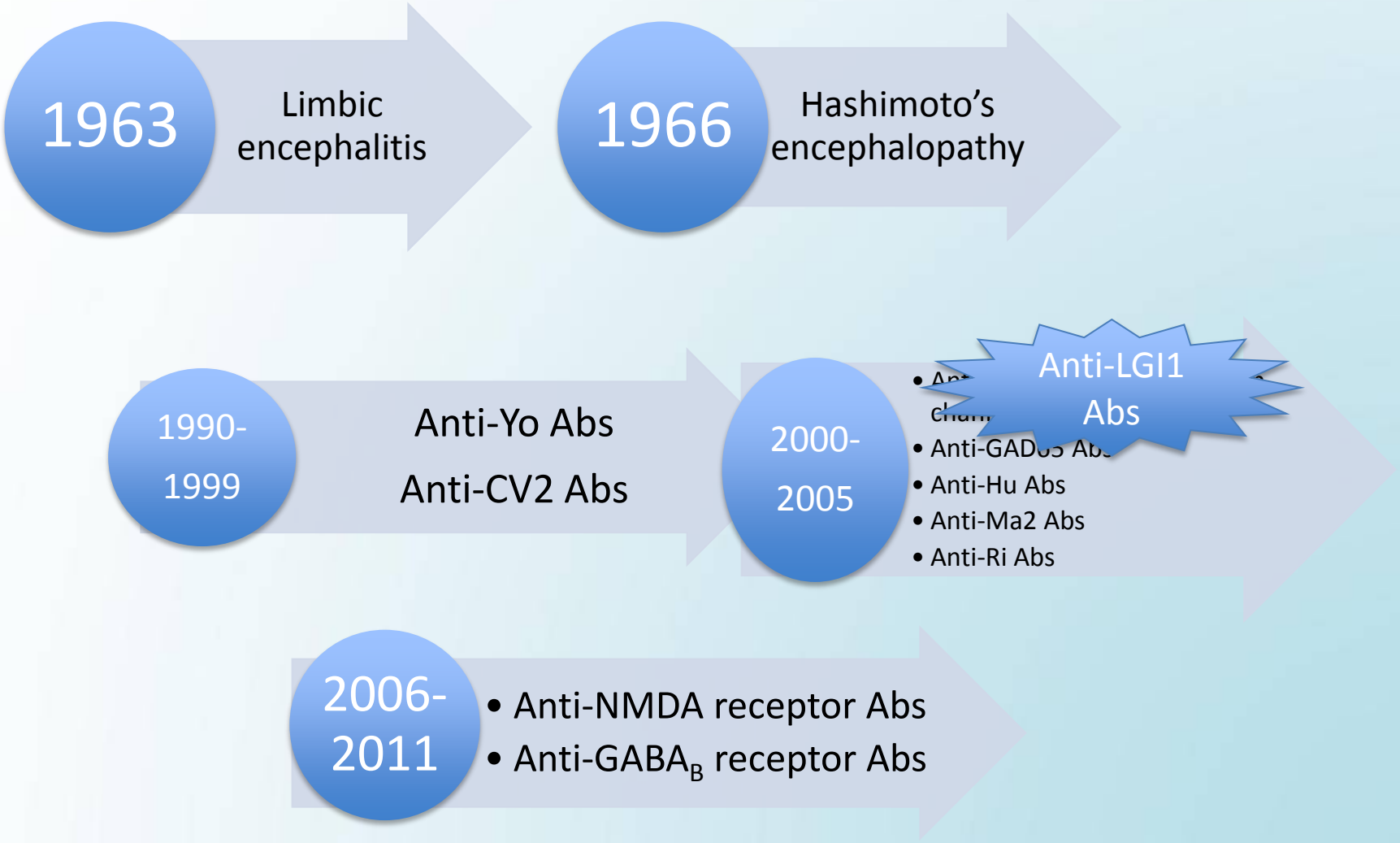
Historical perspective

Lord Brain (later Baron)

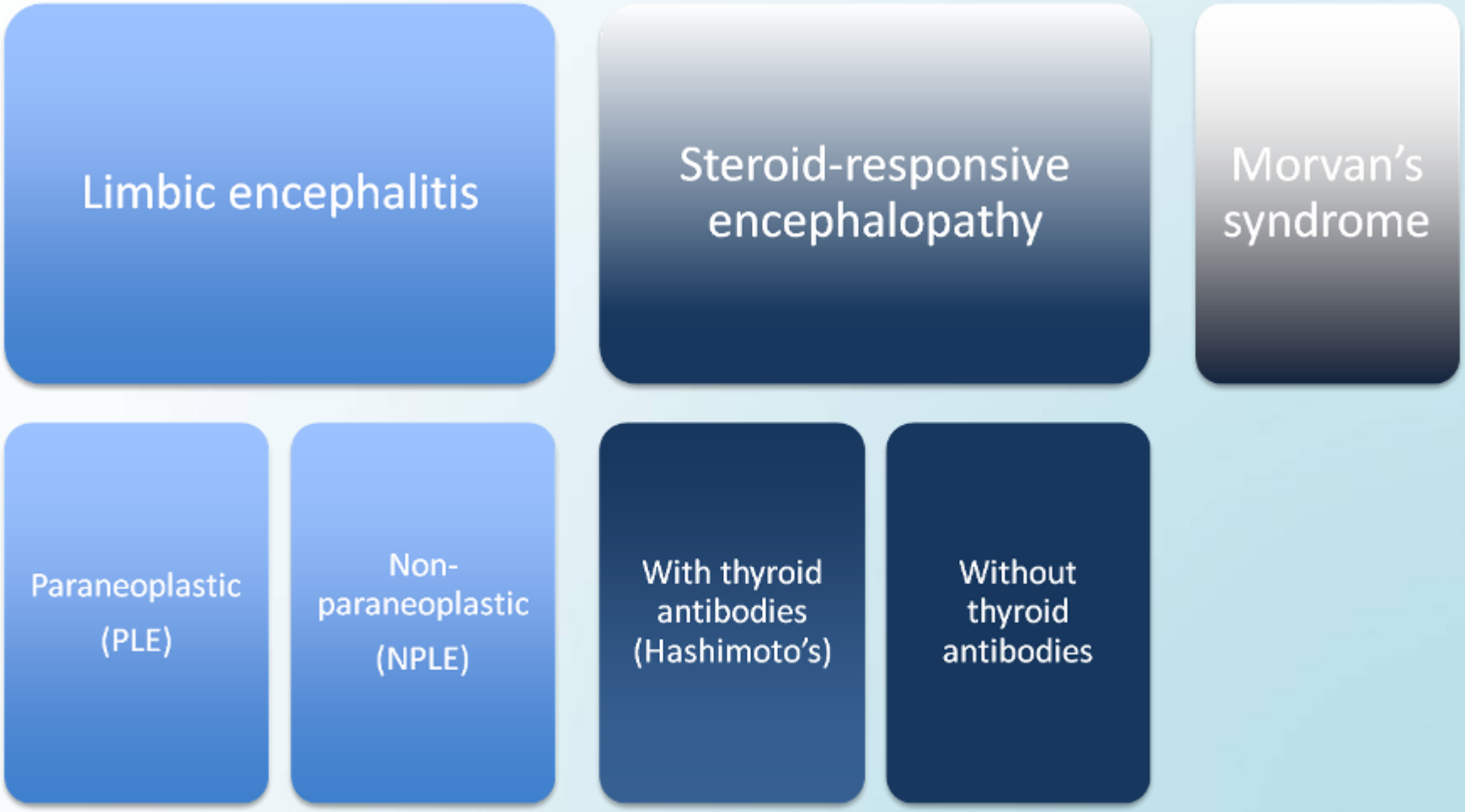


Dr Hakaru Hashimoto

The evolution of an entity



Autoimmune encephalitis – clinical classification



Vernino et al. The Neurologist. 2007

Clinical characteristics

	Paraneoplastic LE	LE with VGKC antibody	Morvan syndrome	SREAT
# of reported cases	>100	~20	~15	~70
Onset (years)	50–75	44–79	37–76	12–84
Gender M:F	1:1.2	3:1	9:1	1:4
Memory loss	+++	+++	++	++
Seizures	65%	67%	No**	50%
Hallucinations	Occasional	Occasional	Common	Uncommon
Insomnia	No	No	+++	+/−
Hyperhidrosis	No	With seizures	++	No
Myokymia	No	No	++	No
Tremor	No	No	No	++
VGKC Antibody	+	+++	+++	No
Thyroid antibody	20%	20%	ND	100%
High CSF protein	80%	40%	50%	80%
Hyponatremia	25%	80%	ND	Uncommon
MRI	Increased signal in mesial temporal lobes	Increased signal in mesial temporal lobes	Normal	Normal (60%) or non-specific changes
EEG	Slowing and epileptiform discharges	Slowing and epileptiform discharges	Normal or mild slowing	Slowing and epileptiform discharges
Response to corticosteroids	Partial response in some pts	++	+	+++

Anti-neuronal antibodies and cancer

Antibody	Predominant tumors	CNS syndromes	Antibody positive patients without cancer[a] (%)	Frequency in cancer without PNS[a] (%)
Hu (ANNA1) [7]	Small cell lung cancer (SCLC)	Encephalomyelitis Paraneoplastic cerebellar degeneration (PCD) Limbic encephalitis Brainstem encephalitis	2	16
CV2 (CRMP5) [8]	SCLC, thymoma	Encephalomyelitis Chorea PCD Limbic encephalitis	4	9
Amphiphysin [9]	Breast, SCLC	Stiff-person syndrome Myelopathy and myoclonus Encephalomyelitis	5	1
Ri (ANNA2) [10]	Breast, SCLC	Brainstem encephalitis Opsoclonus myoclonus	3	4
Yo (PCA1) [11]	Ovary, breast	PCD	2	1
Ma2 [12]	Testicular	Limbic encephalitis Brainstem encephalitis	4	0

Graus et al. J Neurol. 2010.

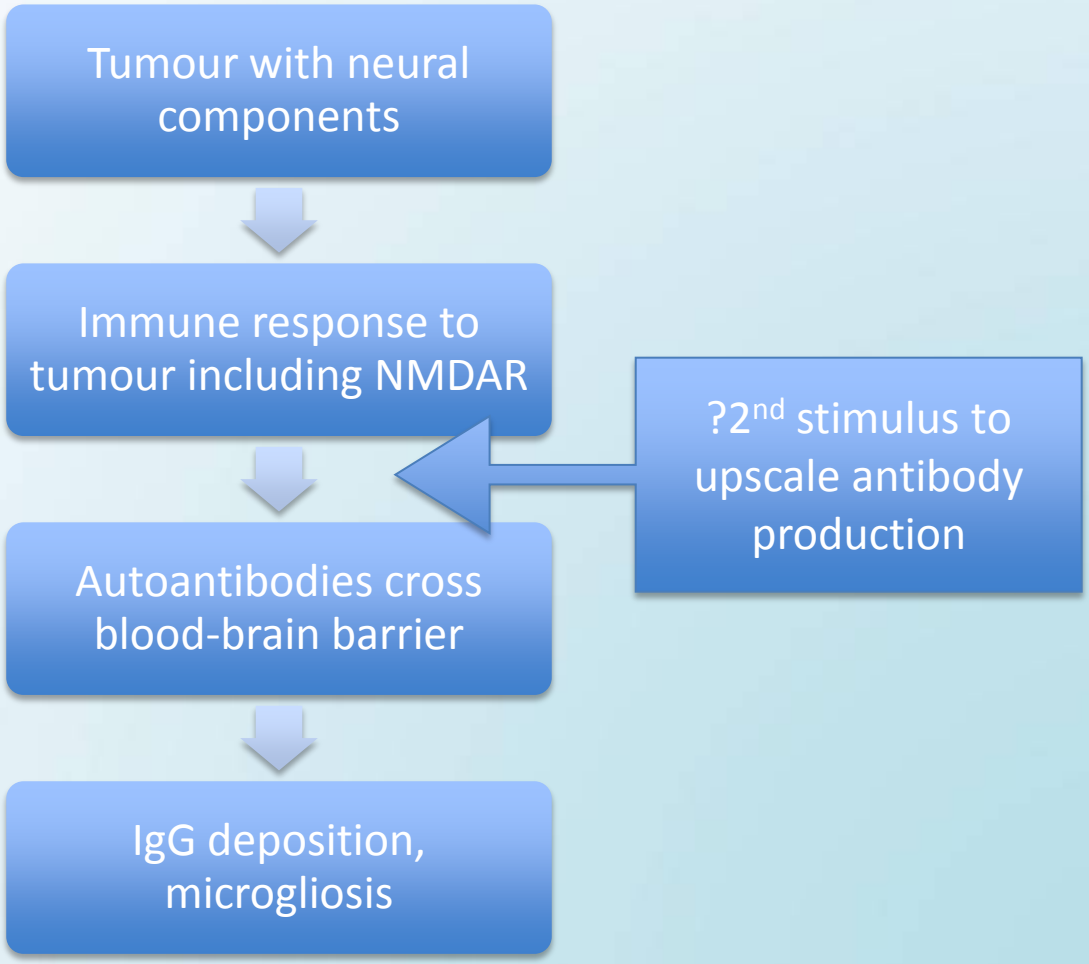
NMDA receptor Ab encephalitis

The new player on the block

- First described 2007
  - Case series young women with teratomas
  - 8/10 improved with Rx of cancer
- >100 cases identified within 12 months
  - Only 25% paraneoplastic
  - 20% have “infectious” prodrome
    - Fever, headache
- 15-25% have relapses
  - Less common if paraneoplastic

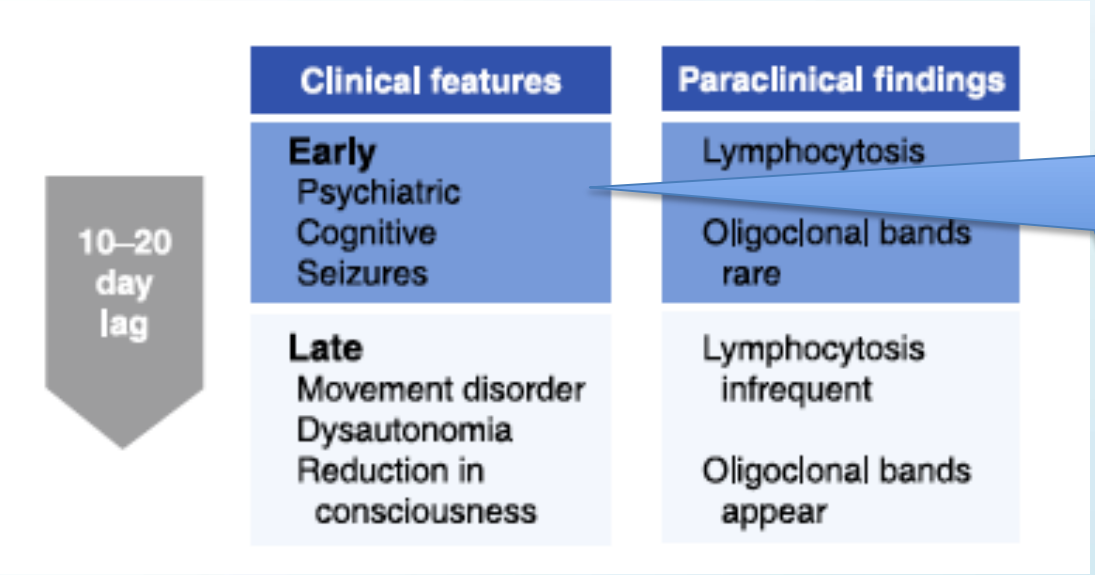
Dalmau et al. Lancet Neurol. 2008

Pathophysiology of NMDAR



Irani et al. Curr Neurol Neurosci Rep. 2011.

Clinical features



- Many require ICU care for sedation / resp
- MRI – often normal (89%), non-specific
  - Early: hippocampi, white matter T2/FLAIR
  - Late: subcortical

Irani et al. Brain. 2010.

Expanding spectrum of disease

- Paediatric cases (>100 described, inc age 2)
- First episode psychosis
- Behavioural disturbance in adolescent girl
- Encephalitis lethargica
- Pure epileptic syndrome

Dale et al. Ann Neurol. 2009.
Zandi et al. J Neurol. 2010.
De Nayer et al. Biol Psych. 2009.

Treatment

- Aim is to reduce NMDAR antibody levels
- Paraneoplastic
  - Tumour removal
  - Chemotherapy
  - Immunotherapy
- Non-paraneoplastic
  - Steroids
  - Plasma exchange
  - IVIg
  - +/- Rituximab, cyclophosphamide

But do we really need to know all this?

Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study

Julia Granerod, Helen E Ambrose, Nicholas W S Davies, Jonathan P Clewley, Amanda L Walsh, Dilys Morgan, Richard Cunningham, Mark Zuckerman, Ken J Mutton, Tom Solomon, Katherine N Ward, Michael P T Lunn, Sarosh R Irani, Angela Vincent, David W G Brown, Natasha S Crowcroft, on behalf of the UK Health Protection Agency (HPA) Aetiology of Encephalitis Study Group

Summary

Background Encephalitis has many causes, but for most patients the cause is unknown. We aimed to establish the cause and identify the clinical differences between causes in patients with encephalitis in England.

Lancet Infect Dis 2010; 10: 835–44

Granerod et al. Lancet Inf Dis. 2010.

Inclusion criteria:

A. Altered mental state >24hrs AND 2 of:

1. Fever >38
2. Seizures +/- focal neurology
3. CSF pleocytosis >4/µL (adults), >10 (infants), >14 (neonates)
4. EEG suggestive of encephalitis
5. Brain imaging suggestive of encephalitis

	Confirmed	Probable	Total (%)
Infectious cause (n=86 [42%; 95% CI 35–49%])			
Herpes simplex virus	36	2	38* (19)
Mycobacterium tuberculosis	1	9	10 (5)
Varicella zoster virus	9	1	10 (5)
Streptococci	2	2	4† (2)
Enteroviruses	3	..	3 (1)
Dual infection	3	..	3‡ (1)
Streptococcus pneumoniae	3	..	3 (1)
Influenza A	..	2	2 (1)
Neisseria meningitidis	2	..	2 (1)
Toxoplasma gondii	2	..	2 (1)
Coxiella burnetii	..	1	1 (0·5)
Epstein-Barr virus	..	1	1 (0·5)
Enterococcus faecium	1	..	1 (0·5)
Human herpesvirus-6	..	1	1 (0·5)
HIV	1	..	1 (0·5)
JC virus	1	..	1 (0·5)
Listeria monocytogenes	1	..	1 (0·5)
Pseudomonas spp	1	..	1 (0·5)
Sclerosing subacute panencephalitis (measles)	1	..	1 (0·5)
Immune-mediated cause (n=42 [21%; 95% CI 15–27%])			
Acute disseminated encephalomyelitis	23	..	23 (11)
NMDA receptor antibodies	9	..	9 (4)
VGKC antibodies	7	..	7 (3)
Secondary to systemic vasculitis	1	..	1 (0·5)
Multiple sclerosis	1	..	1 (0·5)
Paraneoplastic		..	1 (0·5)
Unknown cause (n=75 [37%; 95 -44%])			
Unknown		..	75 (37)
Total			203

15/16 immunocompetent
Evenly age-distributed

Additional interesting points

- CSF white cell count normal in 5/16 cases
  - Median = 22/µL
- CSF protein normal in 9/16
- CSF:serum glucose <0.5 in 4/15
- 1/16 made good recovery
  - 3 died, 6 severely disabled

Is it time to move beyond California?

Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis

M. S. Gable · S. Gavali · A. Radner · D. H. Tilley · B. Lee · L. Dyner · A. Collins · A. Dengel · J. Dalmau · C. A. Glaser

- California Encephalitis Project now incorporates testing for NMDAR Abs if dyskinesias / movement disorders
- Tested 20 patients, 50% positive!

Eur J Clin Microbiol Infect Dis. 2009.

Key points

- Autoimmune encephalitis encompasses heterogeneous group
  - Exclusion of infection is often our priority but earlier immunotherapy is probably better
  - An exact diagnosis is usually not acutely possible
- Expanding range of anti-neuronal antibodies
  - Some are highly specific and worth considering
- NMDAR antibody encephalitis is likely under-recognised yet readily treatable