Metabolic and autoimmune causes of cognitive impairment

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Outline

1. Metabolic causes
   A. severe hypoglycaemia
   B. primary hyperparathyroidism
   C. hypothyroidism
   D. chronic renal failure
   E. acquired hepatocerebral degeneration
   F. Vitamin B12 deficiency
2. Autoimmune causes
   A. limbic encephalitis
      i. paraneoplastic
      ii. non-paraneoplastic
   B. SREAT ("Hashimoto's encephalopathy")
   C. congophilic amyloid angiopathy – related leukoencephalopathy

1A) Hypoglycaemia

– blood glucose ≤ 3.3 mM + suggestive symptoms

– "severe" if requires assistance of another person

(Bauduceau B, et al. Diab Metab 2010; 36 Suppl 3: S106-111)

– children, elderly, and those with type I diabetes most susceptible

i) *very* severe hypoglycaemia → hippocampal > cortical neuronal loss (humans, rodents)

– damage exacerbated by post-event *hyper*glycaemia

1A) Hypoglycaemia

ii) severe hypoglycaemia in late middle-age predisposes to dementia up to 27 years later:

Severe hypos	Increased risk of dementia
1	26%
2	80%
3	94%

(Whitmer RA, et al. JAMA 2009; 301: 1565-1572)

1A) Hypoglycaemia (continued)

iii) recurrent moderate hypoglycaemia

– Diabetes Control and Complications Trial and EDIC study showed:

- moderate hypos do not cause cognitive decline over many years ("preconditioning"), but
- may predispose to damage with more severe attacks (decreased glucose autoregulation and awareness)

(McNay EC, Cotero VE. Physiol Behav 2010; 100: 234-238)

1B) 1° hyperparathyroidism

- common in late middle and old age (~ 1 in 500 women, 1 in 2,000 men)
- clue: ↑Ca^{2+} and Cl^-: PO_4^- ≥ 33
- then: PTH high for level of Ca^{2+}
- 39 women with mild 1° HPT pre- and $^6/_{12}$ post-surgery:
  - ↓ logical memory, selective reminding, and non-verbal abstraction – resolved to baseline after surgery
  - ↑ depression and anxiety – also improved, but cognitive changes independent of mood/anxiety

(Walker MD, et al. J Clin Endocrinol Metab 2009; 94: 1951-1958)

1B) 1° hyperparathyroidism (continued)

- 111 patients with 1° HPT:
  - slowed cognition/psychomotor speed, memory impairment, depression

(Benge JF, et al. J Int Neuropsychol Soc 2009; 15: 1002-1011)

- 47 patients with 1° HPT
  - 13% (6) had impaired Stroop performance pre-operatively
  - resolved in $^{5}/_{6}$ post-operatively

(Mittendorf EA, et al. Endocrine Practice 2007; 13: 338-344)

1B) 1° hyperparathyroidism (continued)

- *may* even be severe enough to mimic CJD or AD, but be fully reversible (case reports)

  (Chadenat M, et al. Rev Neurologique 2009; 165: 185-188; Papageorgiou SG, et al. Clin Neurol Neurosurg 2008; 10: 1038-1040)

1C) Hypothyroidism

i) overt hypothyroidism (↑ TSH, ↓ T_4)

– impaired spontaneous delayed verbal recall (only)

– improves with treatment by 3 months

(Miller JK, et al. J Neuropsychiatry Clini Neurosci 2007; 19: 132-136)

1C) Hypothyroidism (continued)

ii) subclinical hypothyroidism (↑ TSH, normal T_4)

– most studies show no impairment, but

– randomised study of lower *vs.* normal T_4 replacement in overt hypothyroidism showed impaired working memory after 12 weeks

(Samuels MH, et al. J Clin Endocrinol Metabol 2007; 92: 2545-2551)

– fMRI shows alteration during a working memory task

(Zhu DF, et al. Brain 2006; 129: 2923-2930)

1D) Chronic renal failure

- those with GFR < 60 ml/min/m^2 (moderate impairment) and no neurological co-morbidities had:
  - ↓ total acquisition and retention on WLMT's
  - ↓ cognitive inhibition and set-shifting

  (Thornton WL, et al. J Intl Neuropsychol Soc 2007; 13: 344-353; Gelb S, et al. Nephrol Dialysis Transplant 2008; 23: 1032-1038)

1D) Chronic renal failure (continued)

- severity of CRF correlates with degree of impairment of:
  - attention/immediate memory
  - processing speed

  (Kurella M, et al. J Am Soc Nephrol 2005; 16: 2127-2138)

  Review of CRF and cognition: Koushik NS, et al. Neuropsychol Rev 2010; 20: 33-51

1E) Acquired (non-Wilsonian) hepatocerebral degeneration

Review: Meissner W, et al. Handbook Clin Neurol 2011; 100: 193-197

- typically associated with porto-systemic shunting; LFT's not *necessarily* abnormal
- motor features usually present – include:
  - ataxia
  - movement disorders (parkinsonism, chorea, others)
  - occasionally, myelopathy

1E) Acquired (non-Wilsonian) hepatocerebral degeneration (continued)

- cognitive deficits – impairments of:
  - psychomotor speed
  - visual search
  - sequencing

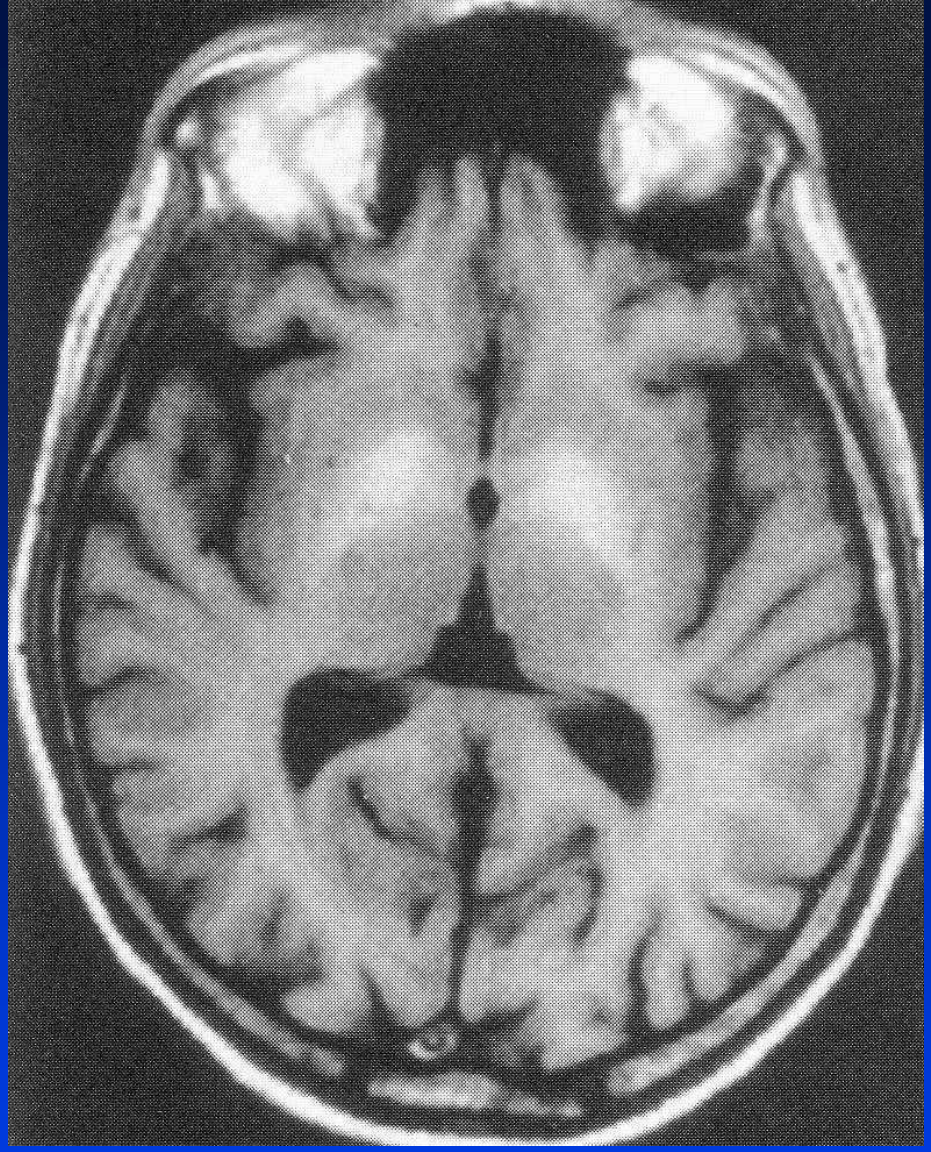
  (other domains reported to be unaffected)

(Stracciari A, et al. Metabol Brain Dis 2008; 23: 155-160)

1E) Acquired (non-Wilsonian) hepatocerebral degeneration (continued)

- Typical (but not diagnostic) MRI appearance
  - high T_1 signal in GPi
  - ± high T_1 signal in caudate, putamen, internal capsule, midbrain, cerebellum

    (due to manganese accumulation)



Grossman RI, Yousem DM. Neuroradiology. 2nd Edn. Mosby Inc ; Philadelphia, 2003

Fig. 8-25 Hyperalimentation-related changes. Note the bilateral increased signal intensity in the globus pallidus on this T1W1. The apparent cause of the hyperintensity is thought to be related to manganese metabolism, which is abnormal in patients undergoing hyperalimentation.

1F) Vitamin B12 deficiency*

- cognitive impairment typically accompanied by neuropathy and/or myelopathy
- of 36 patients with neurological symptoms of B12 deficiency:
  - $^{18}/_{36}$ had cognitive impairment, but
  - only $^{1}/_{18}$ had cognitive impairment *without* neuropathy and/or myelopathy
  - P300 changes reversed with replacement

  (Kalita J, Misra UK. J Neurol 2008; 255: 353-359)

*leaving aside the issue of hyperhomocysteinaemia

1F) Vitamin B12 deficiency (continued)

- $^{12}/_{19}$ patients with dementia and low B12 improved over one year with treatment; $^{7}/_{19}$ declined (presumed AD)
- compared with those who worsened, those who improved had (at baseline):
  - more psychotic symptoms
  - ↓ concentration
  - ↓ visuospatial performance
  - ↓executive function

1F) Vitamin B12 deficiency (continued)

BUT *no*

- language impairment
- ideomotor apraxia
- and less delayed recall problems

(Osimani A, et al. J Geriatr Psychiatr Neuro 2005; 18: 33-38)

1F) Vitamin B12 deficiency (continued)

- some may present as bvFTD, and be fully reversible (*e.g.* Blundo C, et al. Neurol Sci 2011; 32: 101-105; Adkal G, et al. Neurocase 2008; 14: 147-150)
- but others find dementia with low B12 levels to be much less responsive to replacement

  (van Dyck CH, et al. Intl Psychogeriatr 2009; 21: 138-147)

2Ai) Paraneoplastic limbic encephalitis

- age range – teens-70's (usually 50's-70's)
- M : F = 1 : 1.2
- presentation – triad of:
  - amnesia (anterograde episodic memory)
  - temporal lobe seizures ($^2/_3$); all have focal EEG changes
  - neuropsychiatric features (depression, psychosis, personality changes)

2Ai) Paraneoplastic limbic encephalitis

- diagnosis
  - MRI – (often) non-enhancing increased T_2 signal in antero-mesial temporal cortex / hippocampus / amygdala, ± insula / hypothalamus

    (Note: must do *coronal* FLAIR – may be missed on axial)
  - CSF – rule out HSVE (Note: may be 14-3-3 positive)
  - autoantibodies (not all easily available)
  - body imaging: PET scan, testicular ultrasound
- treatment
  - steroids, treat malignancy, immunoabsorbtion (often left with deficits)

2Ai) Paraneoplastic limbic encephalitis

– small cell lung cancer	- Hu/ANNA-1; CRMP-5/ CV2; Lig1; amphiphysin
– testicular cancer, non-SCLC	- Ma-2
– ovarian teratoma	- NR1/NR2 (NMDA receptor)
– thymoma	- VGCC; VGKC; CRMP-5/ CV2; GAD
– others (breast, lymphoma, NSCLC)	- VGCC; (Hu/ANNA-1; CRMP-5/CV2)

(Dalmau J, Rosenfeld MR. Lancet Neurology, 2008)

2Aii) Non-paraneoplastic limbic encephalitis

- "anti-VGKC" (80% of "anti-VGKC" cases)
  (clue – hyponatraemia in 80%)
- limbic encephalitis (anti-Lig1)‡
- Morvan's syndrome*/encephalitis (anti-CASPR2)*

‡ only ~10% are paraneoplastic

* also causes neuromyotonia (Isaac's syndrome)

Anti-NMDAR encephalitis

- commonest immune-mediated encephalitis after ADEM (~4% of all encephalitis in UK)
- peak early 20's; occasional cases to 70's
- ~50% paraneoplastic (ovarian teratomas); 10% male
- "psychosis", amnesia, seizures, coma
- complex, repetitive abnormal movements (orofacial, + dystonic/choreiform), 85%
- autonomic instability 70%
- hypoventilation 65%

2B) SREAT

- other autoimmune causes of dementia
  - "Hashimoto's encephalopathy" (SREAT)
  - lupus cerebritis
  - Sjögren's syndrome

2B) SREAT ("Hashimoto's encephalopathy")

Reviews: *Mocellin R, et al. CNS Drugs 2007; 21: 799-811*
Schiess N, et al. Ann NY Acad Sci 2008; 1142: 254-265

- age range 12-84 (mean ~ 56)
- M : F ≈ 1 : 4 – "defined" by ↑ anti-TPO (microsomal) Ab's, but these are found in 10-20% of controls

2B) SREAT ("Hashimoto's encephalopathy")

- presentation – fluctuating, relapsing – remitting disorder with:
  - cognitive impairment/coma
  - stroke-like episodes/transient aphasia (80%)
  - seizures (60%)
  - neuropsychiatric symptoms
  - tremor (80%, gait ataxia (65%), myoclonus

    (% from Mayo Clinic series of 20 cases; *all* initially misdiagnosed)

(Castillo P, et al. Arch Neurol 2006; 63: 197-202)

2B) SREAT ("Hashimoto's encephalopathy")

- investigations:
  - CSF protein raised (~ 80%) but pleiocytosis (cells) uncommon (~ 25%)
  - MRI normal or minor, irrelevant abnormalities (~ 75%)
  - EEG abnormal in > 90% (usually diffuse slowing)

Limbic encephalitis and SREAT
(after Dr. S. Vernino, U. Texas S.W. Medical Centre)

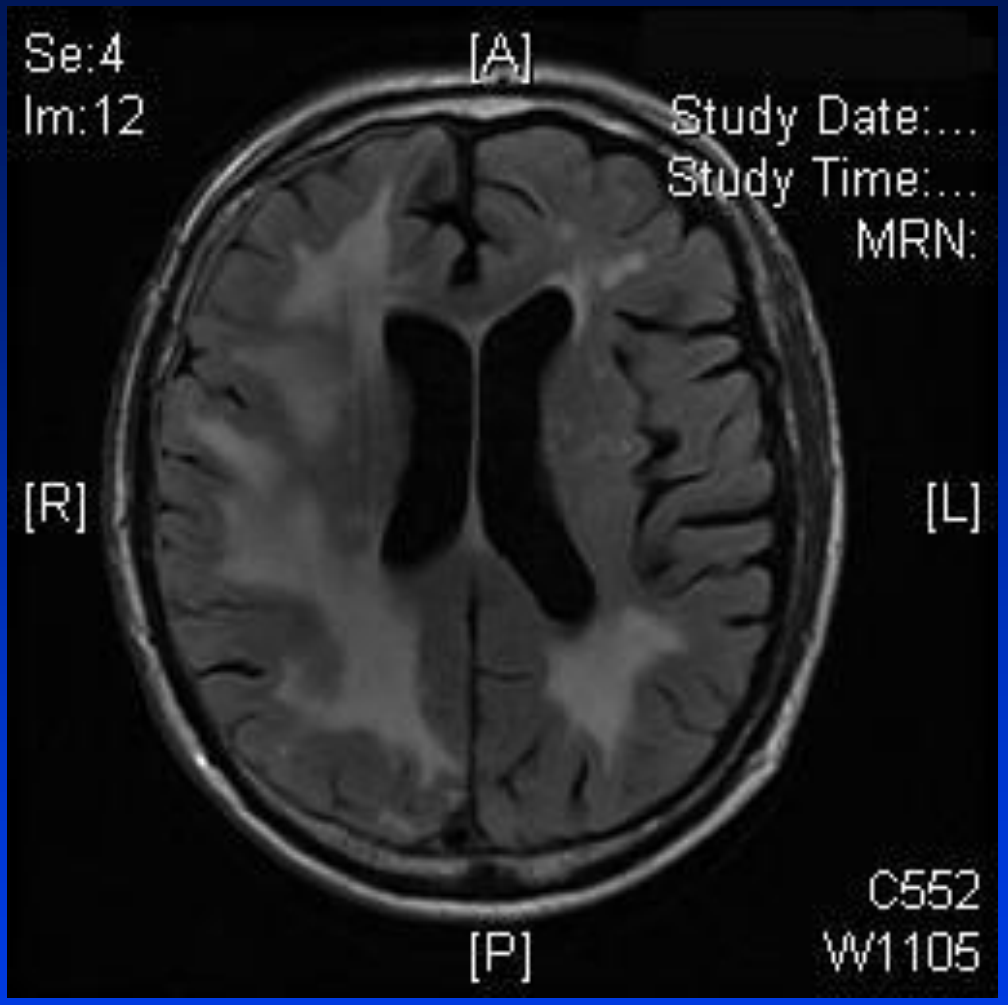
	Paraneoplastic limbic encephalitis	Non-paraneoplastic limbic encephalitis with "VGKC" (Lig1) abnormalities	SREAT
amnesia	+++	+++	++
seizures	65%	67-80% (tonic)	50%
thyroid abnormalities	20%	20%	100%
high CSF protein	80%	40%	80%
hyponatraemia	25%	80%	uncommon
MRI	$\uparrow T_2$ mesial temporal	$\uparrow T_2$ mesial temporal	normal (60%) or non-specific WM
EEG	slowing, epileptiform	slowing, epileptiform	slowing, epileptiform, or normal
response to steroids	partial, in some	++	+++

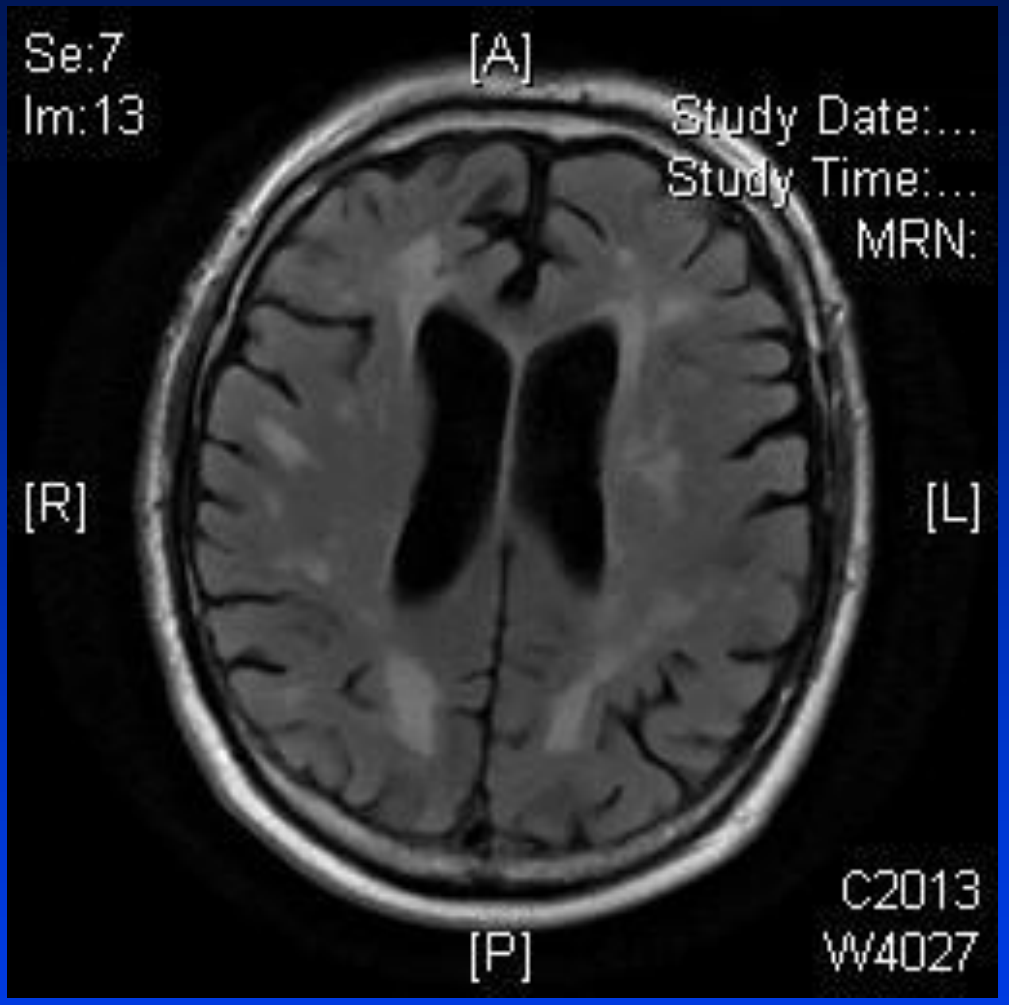
2C) Congophilic amyloid angiopathy – related leukoencephalopathy

- unusual variant of CAA presenting with:
  - leukoencephalopathy on MRI with
  - subacute encephalopathy, and/or
  - headache, and/or
  - seizures, and/or
  - focal neurological symptoms/signs

Pre-steroids

Post-steroids





CAA – Inflammatory form

2C) Congophilic amyloid angiopathy – related leukoencephalopathy

- most (77%) are ApoE ε4/ε4 homozygous (compared with 5% for "ordinary" CAA)
  (Kinnecom C, et al Neurology 2007; 68: 1411-1416)
- may be non-vasculitic (perivascular) or vasculitic
- most respond to steroids, but may relapse

  (Perhaps related to the leukoencephalitis seen in the first Aβ immunisation trials?)