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 \( \leq 3.3 \text{ mM} \) + suggestive symptoms
– “severe” if requires assistance of another person

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

i) very severe hypoglycaemia \( \rightarrow \) hippocampal > cortical neuronal loss (humans, rodents)
– damage exacerbated by post-event hyperglycaemia
1A) Hypoglycaemia

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

<table>
<thead>
<tr>
<th>Severe hypos</th>
<th>Increased risk of dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26%</td>
</tr>
<tr>
<td>2</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>94%</td>
</tr>
</tbody>
</table>

(Whitmer RA, et al. JAMA 2009; 301: 1565-1572)
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: $\uparrow$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:
  - $\downarrow$ logical memory, selective reminding, and non-verbal abstraction – resolved to baseline after surgery
  - $\uparrow$ depression and anxiety – also improved, but cognitive changes independent of mood/anxiety

1B) $1^\circ$ hyperparathyroidism (continued)

- 111 patients with $1^\circ$ HPT:
  - slowed cognition/psychomotor speed, memory impairment, depression

- 47 patients with $1^\circ$ HPT
  - 13% (6) had impaired Stroop performance pre-operatively
  - resolved in $\frac{5}{6}$ post-operatively
1B) 1° hyperparathyroidism (continued)

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

1C) Hypothyroidism

i) overt hypothyroidism (↑ TSH, ↓ T₄)
   – impaired spontaneous delayed verbal recall (only)
   – improves with treatment by 3 months

ii) subclinical hypothyroidism (↑ TSH, normal T₄)

– most studies show no impairment, but

– randomised study of lower vs. normal T₄ replacement in overt hypothyroidism showed impaired working memory after 12 weeks


– fMRI shows alteration during a working memory task

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

1D) Chronic renal failure (continued)

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


1E) Acquired (non-Wilsonian) hepatocerebral degeneration


• 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)

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

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

(due to manganese accumulation)
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:
  - \( \frac{18}{36} \) had cognitive impairment, but
  - only \( \frac{1}{18} \) 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
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

1F) Vitamin B12 deficiency (continued)

- 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 ($\frac{2}{3}$); 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")


- 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)

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)*

<table>
<thead>
<tr>
<th></th>
<th>Paraneoplastic limbic encephalitis</th>
<th>Non-paraneoplastic limbic encephalitis with “VGKC” (Lig1) abnormalities</th>
<th>SREAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>amnesia</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>seizures</td>
<td>65%</td>
<td>67-80% (tonic)</td>
<td>50%</td>
</tr>
<tr>
<td>thyroid abnormalities</td>
<td>20%</td>
<td>20%</td>
<td>100%</td>
</tr>
<tr>
<td>high CSF protein</td>
<td>80%</td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td>hyponatraemia</td>
<td>25%</td>
<td>80%</td>
<td>uncommon</td>
</tr>
<tr>
<td>MRI</td>
<td>↑T₂ mesial temporal</td>
<td>↑T₂ mesial temporal</td>
<td>normal (60%) or non-specific WM</td>
</tr>
<tr>
<td>EEG</td>
<td>slowing, epileptiform</td>
<td>slowing, epileptiform</td>
<td>slowing, epileptiform, or normal</td>
</tr>
<tr>
<td>response to steroids</td>
<td>partial, in some</td>
<td>++</td>
<td>+++</td>
</tr>
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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
CAA – Inflammatory form

Pre-steroids

Post-steroids
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?)