ENCEPHALITIS
Aetiology, diagnosis and management

Neil Anderson
Neurology Department
Auckland Hospital
“Neurology was divided in its early stages for purposes of investigation into anatomy, histology, pathology, physiology and clinical neurology. Clinical neurology itself suffered apparent division into organic neurology, the psychoneuroses, psychiatry and neurosurgery largely because of their separate origins. These divisions are artificial and temporary, and will be resolved when all aspects of the subject are put on a firm scientific basis”.
Encephalitis

- Inflammation of the cerebral cortex
- Encephalitis and meningitis often co-exist
- Encephalitis may be diffuse or focal
Clinical Features of Encephalitis

- Acute onset
- Fever
- Headache
- ± Neck stiffness
- Altered mental state
- Change in behaviour
- Seizures
- ± Focal neurological signs
Limbic encephalitis

- Acute or subacute onset
- Severe impairment short-term memory
- Behavioural and psychiatric symptoms
- Acute confusional state, hallucinations
- Complex partial, 2o generalised seizures
- Inflammatory CSF
- MRI: ↑ signal in medial temporal lobes (2/3)
- Neuropathology: Inflammatory cells, neuronal loss, proliferation of astrocytes and microglia in medial temporal lobes
Aetiology

- > 150 pathogens implicated
- Sporadic or epidemic
- Geographic variation in: incidence, spectrum of aetiological agents
- Most common viral pathogens (U.S.A.):
  - EV 70%
  - HSV 15%
  - VZV 6%
  - WNV 3.6%
- Non-viral pathogens (e.g. Rickettsia, Mycoplasma, Bartonella)
- Cause unknown in > 50% of patients
Herpes simplex encephalitis: Auckland experience in 42 patients

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>31</td>
<td>74</td>
</tr>
<tr>
<td>Confusion</td>
<td>28</td>
<td>67</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>25</td>
<td>60</td>
</tr>
<tr>
<td>Seizures</td>
<td>21</td>
<td>50</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>19</td>
<td>45</td>
</tr>
<tr>
<td>Abnormal behaviour</td>
<td>10</td>
<td>24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>41</td>
<td>98</td>
</tr>
<tr>
<td>Abnormal mental state</td>
<td>38</td>
<td>90</td>
</tr>
<tr>
<td>Focal signs</td>
<td>30</td>
<td>71</td>
</tr>
<tr>
<td>Meningism</td>
<td>23</td>
<td>55</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal CT</td>
<td>25</td>
<td>66</td>
</tr>
<tr>
<td>CSF pleocytosis</td>
<td>38</td>
<td>90</td>
</tr>
<tr>
<td>Abnormal EEG</td>
<td>26</td>
<td>93</td>
</tr>
<tr>
<td>Positive HSV DNA in CSF</td>
<td>36</td>
<td>100</td>
</tr>
</tbody>
</table>

McGrath et al, JNNP 1997; 63: 32-6
Herpes simplex encephalitis: Treatment

- Acyclovir 30 mg/kg/day for 14-21 days
- CSF PCR usually negative by 14 days
- ?Prolonged treatment if PCR still positive after 14 days
- Steroids controversial
- Relapses in 5-10%
Long-term outcome after treatment with acyclovir (n = 42)

- Death: 12%
- Vegetative: 2%
- Severe disability: 17%
- Moderate disability: 21%
- Good recovery: 48%

- STM impairment: 70%
- Anosmia: 65%
- Abn. behaviour: 45%
- Dysphasia: 41%
- Epilepsy: 24%
BRAIN
VOL. 83, PART 3.

SUBACUTE ENCEPHALITIS OF LATER ADULT LIFE. MAINLY AFFECTING THE LIMBIC AREAS
BY
J. B. BRIERLEY, J. A. N. CORSELLIS, R. HIERONS, S. NEVIN
(From the Department of Neuropathology, Institute of Psychiatry, Maudsley Hospital, London; Ranwell Hospital, Wickford, Essex; The Brook Hospital, London, and King's College Hospital, London.)

"LIMBIC ENCEPHALITIS" AND ITS ASSOCIATION WITH CARCINOMA
BY
J. A. N. CORSELLIS, G. J. GOLDBERG and A. R. NORTON
Department of Neuropathology, Ranwell Hospital, Wickford, Essex and the Department of Neuropathology, Institute of Psychiatry, London
Anti-Hu
# Paraneoplastic encephalitis:
## Intracellular antigens

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Encephalitis</th>
<th>Clues</th>
<th>Tumour</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu</td>
<td>Limbic</td>
<td>Multifocal disease</td>
<td>SCLC</td>
<td>Poor</td>
</tr>
<tr>
<td>Ma2</td>
<td>Limbic</td>
<td>Young males</td>
<td>Testis</td>
<td>Poor</td>
</tr>
<tr>
<td>CRMP-5</td>
<td>Variable</td>
<td>Chorea, uveitis</td>
<td>SCLC, Thymus</td>
<td>Poor</td>
</tr>
<tr>
<td>Amphiphysin</td>
<td>Variable</td>
<td>Stiff person</td>
<td>Breast SCLC</td>
<td>Unclear</td>
</tr>
</tbody>
</table>
Patient history: 57, F

- Prodromal illness: arthralgias, rash, headache → Rx prednisone
- Weight loss, poor sleep, poor appetite, anxiety
- Δ depression → Rx fluoxetine
- Rapid change in personality and behaviour: pressured speech, poor concentration, restless, hypervigilant, over-familiarity, sexual disinhibition, insomnia, coprophagia
- Echolalia, perseveration, rhyming, punning, disorganised thought processes
- Δ Manic disorder → Rx lithium, risperidone, clonazepam
Past History

- Δ thyrotoxicosis 2000 → carbimazole, radio-iodine → thyroxine
- Hyperechoic cyst right parafimbrial region 2004
- Benign breast lump 2006
- No history of psychiatric disease
Patient history (continued)

- Periods when mute, akinetic, rigid, staring, dystonia, stereotypical movements
- Rx ECT
- Fluctuating blood pressure, pulse rate
- Apnoeic episodes, hypoventilation $\rightarrow$ respiratory acidosis, seizures
- Transfer to intensive care unit for ventilatory support
Investigations

- Blood tests including thyroid antibodies normal
- CSF acellular, normal protein and glucose, no oligoclonal bands
- CT, MRI normal
- EEG: severe generalised abnormality
- “Paraneoplastic panel” (anti-Hu, anti-Ma2) negative
- CT chest, abdomen, pelvis normal
Paraneoplastic Anti-\(N\)-methyl-\(D\)-aspartate Receptor Encephalitis Associated with Ovarian Teratoma

Josep Dalmau, MD, PhD, Eriem Tüxin, MD, Hui-yen Wu, PhD, Jaime Marjuan, MD, Jeffrey E. Kosin, BA, Alfredo Valeschitz, MD, Joachim M. Berding, MD, Haruo Shimazaki, MD, PhD, Reiji Koide, MD, Dale J. Berg, MD, Warren Mason, MD, Lauren H. Samsing, MD, Marc A. Dichter, MD, PhD, Myrna R. Rosenfeld, MD, PhD, and David R. Lynch, MD, PhD
Live rat hippocampal neuron cultures incubated with patient’s serum
(Josep Dalmau)
Patient: Follow up

- Vaginal ultrasound normal
- Bilateral oophorectomy: normal ovaries
- Treatment with:
  - Intravenous immunoglobulin x 2 courses
  - Pulsed iv cyclophosphamide x 6/12
- Gradual but incomplete recovery
- Lives independently, driving
- Appropriate conversation
- ↓ immediate memory
- Loss of insight
- Unable to return to previous occupation
A: Rat brain coronal section
B: Live rat hippocampal neuron
C: HEK293 cells transfected with NR1 and NR2B
D: Co-localisation of antibody reactivity of CSF and monoclonal ab vs NR1
E: Reactivity with monoclonal antibody vs. NR1
Anti-NMDAR Encephalitis: 577 patients

- Age:
  Range 8 months - 85 years
  Median 21
  37% <18, 5% >45

- Gender
  81% female
  39% <12 years old boys
  43% >45 years old men
Anti-NMDAR Encephalitis (577 patients)

Tumours

- 207 (38%) tumours. Mainly in females aged 12-45
- Tumour present in only 6% of girls <12 and 6% of men
- Tumours:
  - ovarian teratoma 94%
  - extraovarian teratoma 2%
  - miscellaneous tumours 4%

Anti-NMDAR encephalitis: typical clinical picture

- Viral-like prodrome
- Acute psychiatric illness: personality change, agitation, confusion, psychosis
- Unresponsive: mute, akinetic, staring, dystonia, catatonia
- Hyperkinetic: orofacial dyskinesias, chorea
- Other clinical features:
  - Impaired short-term memory
  - Seizures
  - Central hypoventilation
  - Autonomic instability
Anti-NMDAR Encephalitis: Presenting symptoms

- Adults: 65% behavioural symptoms
- Children (<12): 50% seizures or movement disorders
- Adolescents: intermediate
- Maximum mRS in first month: mRS 5 in 86%
- ICU admission in 75%

A

Prodrome

- Clinical worsening
  - Agitation, psychosis, hallucinations, memory deficit, speech reduction, with or without seizures
  - Abnormal movements, coma, respiratory failure, with or without dysautonomia

- Clinical improvement

B

Corresponding PCP values:

- 0.01-0.2 μm
- >0.2 μm

C

Pre

Post
Anti-NMDAR Encephalitis: Investigations

- Abnormal MRI 33%
- Abnormal EEG: 90%
- Abnormal CSF: 79%
- Detection of anti-NMDAR antibodies requires incubation of CSF/serum with:
  - sections of rat brain
  - cultured live rat hippocampal neurons
  - non-neuronal cells that express NMDAR
- Sensitivity and specificity less with serum than CSF
- Relevance of IgA and IgM antibody subtype unknown

Patient 2: 17, F (2013)

- Background history:
  - Bipolar affective disorder Rx clozapine
  - Seizures in 2008, 2011; Normal EEG
- Fell off horse 2 weeks before presentation. Normal examination and CT
- Increasingly bizarre behaviour, headaches
- Psychiatry assessment:
  - disorganised thought processes
  - visual hallucinations
  - ataxia
  - involuntary movements
  - hypersalivation
  - hyperthermia
  - rhabdomyolysis (CK > 20,000)
  - decreasing consciousness
- ?Neuroleptic malignant syndrome
- Transferred to ICU 10 days after onset symptoms
Patient 2

- CSF lymphocytosis, but HSV PCR negative
- MRI normal
- Initial treatment
  - iv methylprednisolone
  - Plasmapheresis
  - iv immunoglobulin
- IgG NMDAR antibody in serum and CSF
Laparoscopic salpingo-oophorectomy: ovarian teratoma
Pathogenesis

- Decrease of NMDAR
- Inactivates GABAergic neurons
  - Effect on brainstem central pattern generator
    - Effect on pontine-medullary respiratory network
  - Increases extracellular glutamate, disinhibits excitatory pathways
    - Semirhythmic movements in bulbar, limb, or trunk muscles
    - Breathing dysfunction, hypoventilation
- Frontostriatal syndrome
  - Psychosis, catatonia mutism, rigidity, dystonia
  - Autonomic instability
Anti-NMDAR Encephalitis: Treatment

- First line
  - High dose steroids
  - IV immunoglobulin
  - Plasmapheresis

- Second line
  - Tumour removal
  - Rituximab
  - Cyclophosphamide
Prognosis

- 81% have good outcome at 2 years
- Continue to improve for 18 months
- Early treatment important predictor of outcome
- 12% relapse in first 2 yrs
- Relapse usually less severe and may be monosymptomatic
Can anti-NMDAR encephalitis be misdiagnosed as a primary psychiatric disorder?

- Two approaches to answering the question
- Do some patients with a diagnosis of primary psychiatric disorder have anti-NMDAR antibody?
- Do patients with NMDAR antibody present with a pure psychiatric disorder with neurological features?
Question 1

- Do some patients with a diagnosis of primary psychiatric disorder have anti-NMDAR antibody?
Zandi et al
J Neurol 2011; 258: 686-8

- IgG anti-NMDAR antibody in serum in 3/46 (6%) of patients with first episode of schizophrenia
- Target subunit of antibody (NR1 or NR2) not determined.
- No controls
- Only 1/6 responded to immunotherapy
- Same investigators recently found similar antibodies in 23% of patients unlikely to have an immune-mediated disorder
Masdeu et al
Am J Psychiatry 2012; 169: 1120-1

- 80 patients with first onset of psychosis
- Serum obtained at onset
- Diagnosis of schizophrenia-spectrum illness after 1 year
- 40 controls
- No patient in either group had NR1 IgG NMDAR antibodies
Steiner et al
JAMA Psychiatry 2013; 70: 271-8

- Measured serum anti-NMDAR antibody in 121 patients with schizophrenia, 70 with major depressive disorder, 30 with bipolar disorder and 230 normal controls
- NR1 IgG antibody found in only 2 patients who in retrospect had typical anti-NMDAR encephalitis
- IgA or IgM antibodies, or antibodies against NR2 subunit found in 10/119 patients with schizophrenia and 2/70 with MDD
- Subsequently these antibodies have been found in healthy individuals
Question 2

- Do patients with NMDAR antibody present with a pure psychiatric disorder with neurological features?
571 patients with IgG antibodies against NR1 subunit of NMDAR

23/571 (4%) had an isolated psychiatric episode with no neurological signs: 5 (0.9%) at disease onset and 18 at relapse

Predominant symptoms:
- delusional thinking (74%)
- mood disturbance (mainly mania) (70%)
- aggression (57%)
- auditory and visual hallucinations (47%)
Conclusions

- Isolated psychiatric symptoms, usually in the form of acute psychosis, are rare but can occur at the disease onset or during relapse
- Clues to diagnosis:
  - previous history of “encephalitis”
  - subtle neurological signs
  - abnormal MRI, CSF or EEG
- NMDAR encephalitis virtually never occurs in the absence of one of these clues
- NMDAR encephalitis does not occur in the setting of schizophrenia, major depressive disorder
Autoimmune encephalitis related to cell surface and synaptic antigens

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDAR</td>
<td>Mainly young women, children; characteristic presentation</td>
</tr>
<tr>
<td>LGI 1</td>
<td>Limbic encephalitis, hyponatraemia, myoclonus, RBD</td>
</tr>
<tr>
<td>Caspr2</td>
<td>Peripheral nerve excitability</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;B&lt;/sub&gt;R</td>
<td>Refractory seizures</td>
</tr>
<tr>
<td>AMPA-R</td>
<td>Seizures, psychosis</td>
</tr>
<tr>
<td>mGluR5</td>
<td>Ophelia syndrome, Hodgkin’s disease</td>
</tr>
<tr>
<td>Gly-R</td>
<td>Stiff person syndrome, hyperrekplexia, PERM</td>
</tr>
<tr>
<td>Dopamine2-R</td>
<td>Children, basal ganglia encephalitis</td>
</tr>
<tr>
<td>DPPX</td>
<td>Diarrhoea, weight loss</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;A&lt;/sub&gt;-R</td>
<td>Refractory seizures</td>
</tr>
<tr>
<td>Iglon5</td>
<td>Abnormal sleep movements, abnormal behaviour, ataxia</td>
</tr>
</tbody>
</table>
Henry Maudsley

“Mental disorders are neither more nor less than nervous disease in which mental symptoms predominate, and their entire separation from other nervous diseases has been a sad hindrance to progress”.