A U T O I M M U N E  
E N C E P H A L I T I S

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OBJECTIVES

- What is encephalitis
- Causes of encephalitis
  - Infectious vs Immune-mediated
- Autoimmune encephalitis
  - Clinical presentation
  - Work-up
  - Treatment
INTRODUCTION

- Encephalitis
  - Inflammation of the brain
  - Associated with neurological dysfunction

- Causes
  - Primary CNS infection
  - Autoimmune process - ? triggered by infection, vaccination or occult neoplasm
BACKGROUND

- Encephalitis Lethargica
  - Described in 1916 by von Economo
  - Neuropsychiatric signs & sleep disturbance following pharyngitis
  - He initially described big cohort, later sporadic cases
  - Dale (2004) – half of his cohort had Ab to NMDA receptor

- Sydenham Chorea
  - Rheumatic fever
  - Known to be immune mediated
Systemic autoimmune conditions like SLE
  - Known to cause encephalitis
  - Vasculitis
PANDAS – paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection
California Encephalitis project

- Started recruiting patients in 1998
- In patients under 30 years autoimmune encephalitis is more common than infectious encephalitis
INFECTIOUS CAUSES

- Mainly viral
  - Certain viruses are more common in certain areas
- American (CEP)
  - Enterovirus, HSV, VZV, WNV
- Australian (155)
  - HSV, enterovirus, mycoplasma, VZV
- Israeli (44)
  - Mycoplasma, enterovirus, HSV, EBV, HHV6, Influenza A, VZV
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Test</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV</td>
<td>PCR</td>
<td>A common cause in both healthy and immune-compromised patients, with particular predilection for the temporal lobes. Specific anti-viral therapy may be life-saving. Rare cases of secondary anti-NMDAR encephalitis afterwards.</td>
</tr>
<tr>
<td>CMV</td>
<td>PCR</td>
<td></td>
</tr>
<tr>
<td>VZV</td>
<td>PCR</td>
<td></td>
</tr>
<tr>
<td>JE</td>
<td>PCR</td>
<td>Once a leading cause in East Asia, but declining due to vaccination programs.</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>PCR</td>
<td>Other, non-polio, strains may also be neurotropic and it is a relatively common cause of encephalitis.</td>
</tr>
<tr>
<td>HHV6</td>
<td>PCR</td>
<td>Important cause in transplant patients. 1% of persons have HHV-6 in their genome, so PCR test can be misleading.</td>
</tr>
<tr>
<td>HHV7</td>
<td>PCR</td>
<td>Rare cause in immune compromised patients.</td>
</tr>
<tr>
<td>Neuroborreliosis (Lyme disease)</td>
<td>Serology</td>
<td>Manifestations include meningitis, encephalitis, radiculitis, cranial neuritis, and peripheral neuropathy.</td>
</tr>
<tr>
<td>WNV (West Nile)</td>
<td>PCR, Serology</td>
<td>Widely distributed mosquito-born flavivirus. Most infections asymptomatic or minimally symptomatic. Encephalitis is the most common presentation, followed by meningitis and flaccid paralysis.</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Serologies</td>
<td>Most cases are sexually transmitted. Neurological symptoms may occur years or decades after exposure. Manifestations are protean.</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>Latex agglutination antigen test, culture</td>
<td>More often presents with meningitis in patients with AIDS and other immune-compromised states. CSF opening pressure may be marked elevated.</td>
</tr>
<tr>
<td>Aspergillus fumigatus</td>
<td>Culture, biopsy, antigen ELISA and other methods</td>
<td>Disseminated CNS aspergillosis is mostly in immune compromised (transplant patients), and pathology usually involves basal ganglia and/or thalami.</td>
</tr>
<tr>
<td>Mucor</td>
<td>Culture, biopsy (ideally for nasal involvement)</td>
<td>May affect both immunocompromised and immune intact persons. Prognosis is grim.</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Chest X-ray, PPD, Serology</td>
<td>In one study the second most common cause of infectious temporal lobe encephalitis behind HSV. May also present with Rhombencephalitis.</td>
</tr>
<tr>
<td>Listeria</td>
<td>Culture</td>
<td>Rhombencephalitis and meningitis are the two main manifestations.</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>Culture</td>
<td></td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Serology</td>
<td>Classically, a common cause of brain lesions in patients with AIDS.</td>
</tr>
</tbody>
</table>
IMMUNE-MEDIATED ENCEPHALITIS

- White matter – demyelinating
  - ADEM, NMO, MS, transverse myelitis
- Grey matter
  - Sydenham chorea, PANDAS, opsoclonus-myoclonus, cerebellitis, Rasmussen’s encephalitis, SLE
- Grey & white matter
  - Vasculitis, MAS, Aicardi-Goutieres
- Specific neuronal pathways & Muscle
  - Channelopathies, MG, GBS, Poly-/Dermatomyositis, Antibody mediated encephalitis
**Autoimmune Encephalitis**

- Antibodies to intracellular Ag
  - Hu, Ma2, GAD
- Antibodies to synaptic receptors
  - NMDA, AMPA, GABAa&b, D2R
- Antibodies to ion channels and other cell surface proteins
  - LGI1, Caspr2, AQP 4, MOG
AUTOIMMUNE ENCEPHALITIS
BACKGROUND

Last 10 years

- Number of non-infectious causes of encephalitis identified
- Ab to neuronal cell surface or synaptic proteins
CLINICAL FEATURES

- Altered level of consciousness / behavioural changes
- Seizures
- Movement disorders
  - Dyskinesia
  - Choreoathetosis
- Ataxia
- Dysautonomia
- Focal neurological deficits
DIAGNOSTIC CRITERIA

GRAUS 2016 - LANCET

- Subacute onset (rapid progression <3 months)
  - Working memory deficit
  - Altered mental status
  - Psychiatric symptoms
- At least 1 of
  - New focal neuro
  - Seizures (new onset)
  - CSF pleocytosis (>5 WBC on CSF)
  - MRI suggestive of encephalitis
- Exclude alternate diagnosis
### Clinical Characteristics of Individual Antibody-Associated Encephalitides in Childhood

<table>
<thead>
<tr>
<th>Autoimmune Encephalitis</th>
<th>Ages Described*</th>
<th>Clinical Manifestations</th>
<th>Associated Tumor</th>
<th>Risk of Relapse</th>
<th>Long-Term Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDAR</td>
<td>20 mo-17 yr</td>
<td>Seizures, behavioral disturbance, aphasia, psychosis, orofacial dyskinesias, catatonia</td>
<td>30% of females with ovarian teratoma</td>
<td>Up to 25% when causative tumor is not identified and removed</td>
<td>80% or greater have full recovery</td>
</tr>
<tr>
<td>VGKC</td>
<td>10 mo-17 yr</td>
<td>Seizures, behavioral disturbance, movement disorders, dysarthria, developmental regression</td>
<td>Neuroblastoma in one case (patient with multiple autoantibodies)</td>
<td>Unknown; reported in single case series as 25% relapse rate in childhood</td>
<td>Unknown, but most reported patients show marked to full recovery</td>
</tr>
<tr>
<td>GlyR</td>
<td>1-14 yr</td>
<td>PERM, seizures, ADEM with ON</td>
<td>None currently reported in childhood</td>
<td>Unknown; reported in single case series as 25% relapse rate in childhood</td>
<td>Unknown; generally considered to have good outcomes</td>
</tr>
<tr>
<td>GABA_A</td>
<td>2-17 yr</td>
<td>Seizures, cognitive and memory alterations, movement abnormalities</td>
<td>Hodgkin’s lymphoma predating encephalitis in one patient</td>
<td>Unknown, but reported in a single pediatric case</td>
<td>Unknown; most have good recovery but residual seizures</td>
</tr>
<tr>
<td>GABA_B</td>
<td>3-18 yr</td>
<td>Seizures, movement disorders, memory loss, delirium, psychosis</td>
<td>None currently reported in childhood</td>
<td>Unknown in childhood</td>
<td>Unknown; majority reported show full recovery</td>
</tr>
<tr>
<td>AMPA</td>
<td>7-8 yr</td>
<td>Seizures, memory loss, behavioral changes</td>
<td>None currently reported in childhood</td>
<td>Unknown in childhood</td>
<td>Unknown</td>
</tr>
<tr>
<td>D2R</td>
<td>4 mo-15 yr</td>
<td>Seizures, lethargy, psychiatric symptoms, dystonia, parkinsonism, chorea, ataxia</td>
<td>None currently reported in childhood</td>
<td>Unknown; reported in case series as 25% relapse rate in childhood</td>
<td>Unknown; a single case series reports full recovery in 40%</td>
</tr>
<tr>
<td>mGluR5 (Ophelia syndrome)</td>
<td>Adolescence</td>
<td>Memory loss, depression, hallucinations, behavior abnormalities</td>
<td>Hodgkin’s lymphoma</td>
<td>Uncommon if treated appropriately</td>
<td>Full recovery with appropriate treatment</td>
</tr>
<tr>
<td>Hu</td>
<td>1-15 yr</td>
<td>Behavioral changes, seizures, posterior cord syndrome, ataxia</td>
<td>Estimated 25% associated with neuroblastoma</td>
<td>Unknown in childhood</td>
<td>Reported patients with continued seizures despite treatment</td>
</tr>
<tr>
<td>Ma1 and Ma2</td>
<td>2-14 yr</td>
<td>Seizures, behavioral changes, memory loss, speech changes</td>
<td>None currently reported in childhood</td>
<td>Unknown in childhood</td>
<td>Reported patients with poor outcomes</td>
</tr>
<tr>
<td>GAD</td>
<td>2-17 yr</td>
<td>Seizures, cognitive decline, psychosis, memory loss, stiff-person syndrome, progressive developmental delay</td>
<td>None currently reported in childhood</td>
<td>Unknown in childhood</td>
<td>Variable outcome potentially related to rapidity of treatment</td>
</tr>
</tbody>
</table>
Anti-NMDA Receptor Encephalitis

- Commonest cause of autoimmune encephalitis in children
- Female > Male
- Paraneoplastic encephalitis
  - > 18 yrs – Strong association with ovarian teratoma 56%
  - <18 yrs only 30%
  - <14 yrs 9%
- Seasonal variation - idiopathic
  - ? Environmental trigger – Influenza A
Risk Factors

- Female
- Age
- Genetic predisposition
  - Higher in African and Asian
  - Identical twins
  - Higher family hx of autoimmunity
- HSV encephalitis & other viral infections
Etiology
NMDA receptors are found in
- Forebrain
- Hypothalamus
- Pituitary
- Limbic system

Glutamate
- Most abundant excitatory NT
- Function in memory & learning
CLINICAL FEATURES

- Prodrome
  - Flu like symptoms

- Early signs
  - Behaviour change – anxiety, agitation, aggression
  - Psychosis – hallucinations & delusions
  - Memory loss
  - Sleep abn
  - Speech abn
  - Movement disorders
  - Seizures

- Late
  - Decreased level of consciousness
  - Rigidity, dystonia & orofacial dyskinesias
  - Autonomic instability
INVESTIGATION

- CSF – cell counts, chemistry, viral studies
  - 94% children had pleocystosis or raised protein
  - May be higher if repeated
- Serum and CSF for anti NMDA Abs
EEG

- 30% extreme delta brush pattern.
- Diffuse slowing
- Epileptiform activity
Imaging (MRI)

- Normal or hyperintensities on T2 FLAIR
- Hippocampus, CC, temporal lobe, parietal cortex, frontal cortex, medulla & spinal cord
- In children only ~ 1/3 abn MRI
FIGURE 2. Fluid-attenuated inversion recovery (FLAIR) white matter hyperintensities shown on magnetic resonance imaging.

The translucent white regions (arrows) in A and B indicate the areas of FLAIR white matter hyperintensities.
Different clinical presentations
- Acquired neuromyotonia
- Morvan’s syndrome (neuromyotonia, cognitive impairment & dysautonomia)
- Limbic encephalitis

Different protein in VGKC complex
- Leucine-rich glioma-inactivated 1 (LGI1) – Limbic encephalitis
- Contactin associated protein like 2 (Caspr2) – Morovan’s
- Contactin 2
CLINICAL FEATURES

- Limbic encephalitis
  - Cognitive decline
  - Refractory seizures
  - Memory loss
  - Acute psychiatric symptoms
- CSF normal, may show pleocytosis
- MRI – abn in mesial temporal, cingulate gyrus, hypothalamus & pituitary
BASAL GANGLIA ENCEPHALITIS

- Previously called Encephalitis Lethargica (hypokinetetic type)
- Clinical features
  - Parkinsonism
  - Dystonia
  - Hypersomnolence
  - Emotional lability
  - OCD
  - ADHD
- D2R Ab
OTHER

- Many other syndromes described
- Other Ab associated Limbic encephalitis
  - AMPA receptor
  - GABA receptor
- Stiff person syndrome (Progressive encephalomyelitis with rigidity and myoclonus)
  - Gly receptor
  - GAD 65 (T1DM)
- Neuromyelitis optica
  - AQP 4 antibodies
  - MOG (myelin oligodendrocyte glycoprotein) antibodies
INVESTIGATIONS

Testing available in SA

- Offered by Ampath
- NMDA panel includes AMPA, GABA, LGI1, CASPR2
- Anti-neuronal panel includes anti-Hu, -Ri, -Yo, -Ma2, -CV2 & -ampiphysin
- Anti-GAD 65
- AQP 4
- Rule out viral causes
- Look for malignancy
- Blood and CSF
- EEG
- Imaging
TREATMENT — GENERAL

- Immune modulation
- Supportive treatment
  - Ventilatory support
  - Manage seizures
  - May worsen with antipsychotics
Suspicion for autoimmune encephalitis based upon:
- Acute or subacute onset of symptoms
- Evidence of CNS inflammation by:
  a) CSF analysis (lymphocytic pleocytosis, elevated oligoclonal bands, or IgG index) and/or
  b) MRI and/or c) neuropathology
- Supportive ancillary testing (e.g., suggestive EEG pattern, elevated CSF neopterin)
- Exclusion of other causes - including infection, trauma, toxic-metabolic, neoplasm

Send autoantibody panel in serum and CSF (if clinically appropriate)

Negative Antibody Testing → Reconsider other etiologies

Positive Antibody Testing

Mild/moderate encephalopathy

- IVMP
  20-30 mg/kg/day (up to 1 gram daily) for 3-5 days

- IVIg
  2 g/kg divided over 2-5 days

Initial Immunotherapy Trial

Severe encephalopathy

Plasma Exchange
5 exchanges over 10 days

Good response → Supportive care
Consider chronic immunosuppression*

Poor response

Secondary Immunotherapy Trial

Plasma Exchange† - or - Rituximab +/- Cyclophosphamide
OUTCOMES

- NMDA
  - About 80% recover
  - Autonomic and seizures recover first
  - Subtle behaviour and cognitive changes may remain

- VGKC
  - About 75% recover
  - Long term – ?

- Children with tumors and autoimmune encephalitis do better than those with the same tumors who don’t have encephalitis
  - ? Earlier presentation
  - ? Antibodies protective

- Early recognition & treatment – improves outcomes
QUESTIONS
SUMMARY

- Autoimmune encephalitis includes a broad spectrum of conditions
- Need to have a high index of suspicion
- Early immunomodulatory treatment results in better outcomes
REFERENCES


