CHAPTER 36

AUTOIMMUNE ENCEPHALITIS AND PSYCHOSIS

This is a rapidly developing field. There are many uncertainties – people are trying to bring together complicated pre-clinical and clinical information.

AUTOIMMUNE ENCEPHALITIS (AIE)

Encephalitis is the result of brain inflammation - the most frequent cause is infection. In the absence of infection - autoimmune encephalitis is the next most frequent cause.

AIE - LIMBIC ENCEPHALITIS

LE is an autoimmune process predominantly involving the limbic system - first described by Brierley et al (1960) – LE has a sub-acute onset with memory loss, confusion, agitation, hallucinations, seizures and sleep disturbance (Ramanathan et al, 2013).

LE is classically described as being paraneoplastic (being associated with neoplasm), most often lung and testicular malignancies. The antibodies are frequently directed against intra-neuronal proteins.

For a mind-numbing list of other forms of AIE, see Graus et al (2016).

AIE – ANTIBODIES AGAINST NEURONAL CELL SURFACE ANTIGENS

“neuronal surface antibodies” (NSAbs; Ramanathan et al, 2013).

NMDA-R Encephalitis

(N-methyl D-aspartate-receptor encephalitis) is the most common encephalitis featuring NSAbs (Dalmau et al 2007; Hermetter et al, 2018).

The NR1 subunit of NMDA receptor is the target. (NMDA receptors are composed of 2 NR1 subunits and 2 NR2 subunits. NR1 antibodies are more common in the hippocampus.)

Antibodies cause a selective decrease in NMDA receptor density. However, this is reversible, and consistent with frequent recovery.
About 80% are young (median age, 20 years) females.

MRI is usually normal, however, in 40% there is transient inflammation of the hippocampus, cerebral or cerebellar cortex.

75% of patients make a good recovery with treatment. 6% of patients have died (it is anticipated the survival rate will improve with greater awareness and earlier appropriate treatments).

**DIAGNOSIS OF AIE**
Psychiatric disorders are the most common symptoms (Steiner et al, 2018).

The first stage often features virus-like symptoms – headaches, lethargy, fevers – then behavioral changes, memory deficits and psychosis in about 2 weeks.

Next, language difficulties, seizures, movement disorders, and autonomic dysfunction – hyperthermia, cardiac arrhythmia, blood pressure instability and coma – calling for ICU management.

EEG – may reveal slow wave activity
MRI – hyperintense signal on T2-weighted/FLAIR
CSF – increased number of lymphocytes

FDG-PET studies have shown cortical hypermetabolism during the acute stage and hypometabolism in later stages of the illness (Pillai et al, 2010).

Antibody detection is not helpful in the early stage, as laboratory results take some days, emphasizing the importance of clinical judgement.

Antibodies mainly affect the medial temporal lobes, amygdala, hippocampus and orbitofrontal cortex. There is rapid removal (reversible) of neurotransmitter receptors from synaptic sites, leading to changes in synaptic and circuit function.

Autopsies demonstrate a shrunken brain, however, if the individual survives, brain atrophy may be reversed (Lizuka et al, 2010).
Treatment
Early treatment with first-line (steroids, plasmapheresis or intravenous immunoglobulins) or second-line (rituximab or cyclophosphamide) immunotherapy is generally associated with a good outcome.

The current author is confused about the place of dopamine-receptor-blocking drugs which are used in the treatment of psychosis. There is evidence they have an anti-inflammatory action, suppressing pro-inflammatory cytokines, IL-1, IL-6, TNF-alpha and INF-gamma, and have been thought useful in treating AIE. However, a recent statement suggests they may be “harmful” (Hermetter et al, 2018).

Tumor screening is essential - found in 1/3. In young females - frequently ovarian teratoma.

PSYCHOSIS AS AN AUTOIMMUNE DISEASE
An early proposal that schizophrenia is an immune disorder came from Heath & Krupp in 1967.

There is a plausible link between the psychoses and autoimmune disorders. NSAbs provide a possible mechanism. When psychosis is present, immunological therapy may produce an excellent outcome (Al-Diwani et al, 2017).

It is early days in this area, but evidence indicates that a small percentage (not all) schizophrenia may be due to autoimmunity/NSAbs.

Lennox et al (2017) studied 228 patients with first-episode psychosis, and 105 healthy controls. Twenty (9%) of patients had NSAbs, compared to 4% of the healthy controls.

Seven (3%) of patients featured NMDAR antibodies, compared to no controls.

Patients with NMDAR antibodies did not differ from patients without NMDAR antibodies.

The only way to detect patients with potentially pathogenic antibodies is to screen all patients with first-episode psychosis.

In this study (Lennox et al, 2017) no patients were diagnosed with encephalitis (on clinical grounds). Presence of NSAbs was not associated with any increased need for care, and immunological treatment was not provided.
Most of the antibodies in this study were directed toward the GluN1(NR1) subunit of the NMDAR. 2/3 of patients presented with psychiatric before neurological symptoms. Other autoimmune encephalitides in this study were associated with autoantibodies to the Gamma-aminobutyric-acid receptor (GABA\textsubscript{A}R) and voltage-gated potassium channel (VGKC)-complex.

In this study NSAbs were detected in only 9% of patients – thus, it is clear that autoimmune processes are not the only pathological events which produce the clinical picture of schizophrenia. It is also very interesting that patients with NSAbs could not be clinically distinguished from those without – and, that 4% of healthy controls carried NSAbs.

Lennox et al (2017) suggested that the only way to detect patients with the potentially pathogenic antibodies is to screen ALL patients with first-episode psychosis.

Scott et al (2018) conducted a prospective study of 113 first episode psychosis patients. 6 had NSAbs. In contrast with the study above, 5 received immunotherapy and 4 of these experienced prompt resolution of psychosis.

2 developed a diffuse encephalopathy with seizures consistent with classical LE.
3 had isolated psychiatric syndromes without other features of encephalitis.
2 had an ovarian teratoma which was removed.

Neuroimaging and EEG did not render abnormal results – this reinforces that although neuroimaging and EEG are listed as diagnostic tools, they are often negative.

Scott et al (2018) remarked there was a low prevalence of NSAbs in schizophrenia, and that early diagnosis and the provision of immunotherapy led to an excellent clinical response.

Other reports of schizophrenia
Zandi et al (2011) - 46 cases of schizophrenia - 3 people had NMDA-R antibodies.
Tsutsui et al (2012) - 51 cases of schizophrenia and schizoaffective disorder - 4 people with anti-NMDAR antibodies. All had failed to respond to standard treatment but had responded to ECT. All were female, 2 had ovarian tumors.
Kelleher et al, (2015) - 80 people with first episode psychosis and found 4 (5%) were serum positive for NMDAR antibodies
Ojeda-Lopez et al (2015) - 59 consecutive patients with catatonic syndrome and found 5 cases of NMDA-R antibodies.

Masopust et al (2015) - 50 antipsychotic naïve patients with a first episode of psychosis and 50 controls. No NMDAR antibodies were found – statistically, this had to happen.
Postpartum psychosis


4 (4%) patients had immunochemistry results suggesting extracellular antigen reactivity. 2 (2%) had NMDAR antibodies (neither had a teratoma). None of the healthy postpartum participants had NSAbs. Thus, this second form of psychosis may also be associated with autoimmune pathology.

Illustration. A 20-year-old woman was admitted to the Royal Hobart Hospital - behaving in a bizarre manner. Initially, we thought she was probably suffering schizophrenia. When asked to write a sentence, she did so in a manner we did not recognize. However, when she was asked to draw a clock-face, it looked very ‘organic’, in the style of a person with dementia/head injury. This was autoimmune encephalopathy with NMDAR antibodies.
APPENDIX

GENERAL CLINICAL STUDIES

Aupy et al (2013): 16 adults (mean age 45.3 ± 10 years) with autoimmune encephalitis
- neuropsychiatric symptoms in 100%
- seizures were observed in 56%
- cancer in 25% (small-cell lung cancer, testis seminoma)
- antibodies detected in 56%
- complete recovery 30% - partial recovery 60% - fatal 10%.

Hacohen et al (2012): 48 children and adolescents with probable autoimmune encephalitis
- antibodies detected in 44%
- cancer detected in 2% (1 individual; ovarian teratoma)
- of those who did not receive immunotherapy only 29% made complete recovery.

OTHER SPECIFIC ANTIBODY STUDIES

- **Anti-AMPA receptor encephalitis**
  (another type of glutamate receptor; Lai et al, 2009)

The most common presentation may be as above, with personality changes followed by seizures, variation in consciousness and autonomic labiality. Sometimes, however, patients present with rapidly progressive abnormal behavior resembling psychosis.

Usually women, 50 years plus. 70% have an underlying tumor – usually lung or breast, that expresses AMPA receptors.

The antigens is the GluR1 and/or GluR2 subunit of the AMPA receptors (GluR1 & 2 levels are high in the hippocampus and other limbic regions).

- **Anti-GABA\(_B\) Receptor Encephalitis**
  (an inhibitory receptor; Lancaster et al, 2009)

Older people, both male and female. 
47% small cell lung cancer (SCLC)
The autoantigen is the B1 subunit of GABA\(_B\) receptor
- **Anti-Voltage-gated potassium channel (VGKC) disorders**
  (peripheral and CNS types; Kleopa et al, 2006)
May or may not be paraneoplastic
Psychiatric and neurological symptoms, including seizure.

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