CHAPTER 36

AUTOIMMUNE ENCEPHALITIS

This is a new field. The current author is not an expert. Definitions are not clear – there is concern the same condition may be known by different names, and different conditions may be known by the same name.

Most important from a psychiatric perspective is a recently described condition involving antibodies to N-methyl-D-aspartate (glutamate) receptors (anti-NMDA-Rs) (Dalmau et al, 2007). But, limbic encephalitis (LE) was described half a century ago, and will be mentioned first.

Site of the antigen
It seems the site of the antigen may separate LE and anti-NMDA-R encephalitis and some other forms of autoimmune encephalitis.

1. **Intra-neuronal proteins (antigens)** occur in LE. Examples include Hu, Ma and Ri.
2. **Neuronal surface antigens** are frequently receptors or synaptic proteins. They are attacked by "neuronal surface antibodies" (NSAbs; Ramanathan et al, 2013).

LIMBIC ENCEPHALITIS (LE)

Limbic encephalitis, (Brierley et al,) was first described in 1960. Unsurprisingly, it is an inflammatory or autoimmune process predominantly involving the limbic system. It 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 antigens are frequently intra-neuronal proteins.

NEURONAL SURFACE ANTIBODY SYNDROMES (NSAS)

Pioneering work in NSAA by Delmau et al (2007) concerned anti-NMDA-R encephalitis. New reports describe new surface antibodies (listed later). It is not clear whether these have different clinical presentations. A general picture follows.

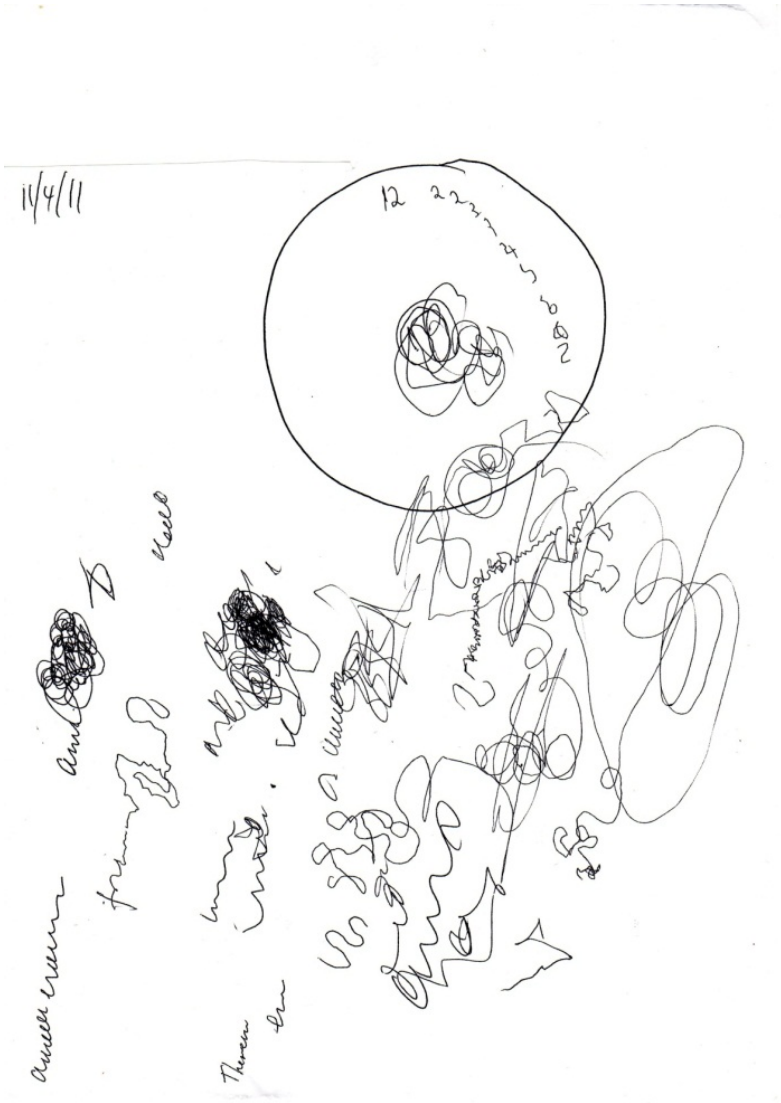

Illustration. A young Indian woman was admitted to hospital, behaving in a bizarre manner. Some of our staff thought she had schizophrenia. When she was asked to write she did so in a manner we did not recognize. However, when she was asked to draw a clock-face, it looked very ‘organic’, in the style of a person with dementia/head injury. She suffered an autoimmune encephalopathy (with anti-NMDA-R antibodies).

Recent reports of autoimmune encephalitis excited and alarmed psychiatrists. They tell of conditions which commence with “flue-like” symptoms, in which the presenting complaints are often delusions and hallucinations, accompanied or followed by odd movements of the face or limbs (dyskinesia), seizures, autonomic dysfunction and possibly death from central hypoventilation (Tidswell et al, 2013).

There is progressive structural damage of the hippocampi, which may lead to severe irreversible cognitive impairment – thus, rapid diagnosis is desirable (Finke et al, 2015). Given the psychotic symptoms, it is not surprising that 30% of patients present or are admitted to psychiatric facilities. Given the possible sudden need for life support and the potential cognitive damage, it is not surprising psychiatrists are a little alarmed.

The condition is more common in women (80%), particularly young (early-20s) but may occur in either gender and at any age. Neoplasms are common, often ovarian teratomas.

More common in some ethnic groups: African, Asian, Latinos.

NSAS are more prevalent than LE, and less commonly paraneoplastic (Lancaster et al, 2013). Thus, unknown immunological triggers are involved. Cross reactivity of antibodies against different antigens can occur (Irani and Vincent, 2012).

Site and action

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 shrunken brain, however, if the individual survives, brain atrophy may be reversed (Lizuka et al, 2010).

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

Therapy

Removal of neoplasm when present (Lancaster, 2011). Hacohen et al (2012) recommend that even in the absence of known antibodies, immunotherapies (corticosteroids, IV immunoglobulins, and plasma exchange) should be provided.

Outcome

Surprisingly, the outcome of NSAS may be good, depending on circumstances and treatment (see below). However, relapse is not uncommon (Guan et al, 2015).

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.

SPECIFIC ANTIBODY STUDIES

- **Anti-NMDA receptor encephalitis**

(a glutamate receptor; Dalmau et al, 2007)

1. Often follows prodrome of viral-like illness, hyperthermia, headache
2. Followed by personality changes which may take individual to a psychiatrist
3. Followed by seizures, dyskinesia, decreased level of consciousness, autonomic instability, hypoventilation.

Usually women

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

75% have 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).

Evidence suggests the NR1 subunit of NMDA receptor as the target autoantigen. (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.

- **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.

Effects of maternal antibodies on fetal development

Studies of mothers of autistic children raise the possibility that maternal antibodies may impact on fetal development. Asymptomatic mothers may have circulating neuronal antibodies that have access to the fetal brain and may affect brain development.

Schizophrenia

There is interest to determine whether some of those who have psychotic symptoms, but no other encephalitic symptoms (seizure, memory deficits and variation in conscious level) carry a receptor antibody. Rosenfeld et al (2012) report that greater than 3% of Anti-NMDA-R cases are

'monosymptomatic'. Probable autoimmune encephalitis may mimic bipolar disorder (Choe, 2012) or schizophrenia.

It is too early to make firm conclusions, but evidence suggests that some people with schizophrenia carry receptor antibodies. Zandi et al (2011) examined 46 cases of schizophrenia and found 3 people with anti-NMDA-R antibodies. Tsutsui et al (2012) studied 51 cases of schizophrenia and schizoaffective disorder and found 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.

Masopust et al (2015) studied 50 antipsychotic naïve patients with a first episode of psychosis and 50 controls. They found no cases positive for antibodies against NMDA-R. However, Kelleher et al, (2015) studied 80 people with first episode psychosis and found 4 (5%) were serum positive for NMDAR antibodies, and Ojeda-Lopez et al (2015) studied 59 consecutive patients with catatonic syndrome and found 5 cases of anti-NMDA-R antibodies.

The future

How much this work is going to help our patients with psychosis (and possibly autism and dementia) is uncertain. After a period of great optimism, at The Lancet Neurology Autoimmune Disorders Conference in 2015, while the spirits of the neurologists remained upbeat, those of the psychiatrists were a little dampened. Nevertheless, this work is destained to contribute significantly to neurology and psychiatry.

Acknowledgement

Prof Ko Tsutsui of the Department of Neuropsychiatry, Akta University, Japan

References

Aupy J, Collongues N, Blanc F, et al. Autoimmune encephalitis, clinical radiological and immunological data. [French] Rev Neurol (Paris) 2013; 169:142-153.

Brierley J, Corsellis J, Herons R, et al. Subacute encephalitis of later adult life mainly affecting the limbic areas. Brain 1960; 83:357-368.

Choe C, Karamatskos E, Schattling B, et al. A clinical and neurobiological case of IgM NMDA receptor antibody associated encephalitis mimicking bipolar disorder. Psychiatry Research 2012, in press.

Dalmau J, Tuzun E, Wu H. et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratomas. Annals of Neurology 2007; 61:25-36.

Guan H, Kong W, Peng H, et al. Clinical characterization of relapsing anti-NMDAR encephalitis 2015, P13, Delegate Program Booklet. The Lancet Neurology, Autoimmune Disorders Conference, March 26-7, Barcelona, Spain.
Hacohen Y, Wright S, Waters P, et al. Paediatric autoimmune encephalopathies. Journal of Neurology, Neurosurgery and Psychiatry 2012, in press.
Finke C, Kopp U, Pajkert A et al. Structural hippocampal damage following anti-N-Methyl-D-aspartate receptor encephalitis. Biological Psychiatry 2015 Feb 26. [Epub ahead of print]
Irani S, Vincent A. The expanding spectrum of clinically distinctive, immunotherapy-responsive autoimmune encephalopathies. Arq Neuropsiquiatr 2012; 70:300-304.
Kelleher E, McNamara P, Whitty P, et al. Clinical implications of screening for NMDAR antibodies in first episode psychosis 2015, P54, Delegate Program Booklet. The Lancet Neurology, Autoimmune Disorders Conference, March 26-7, Barcelona, Spain.
Kleopa K, Elman L, Lang B, Vincent A, Scherer S. Neuromyotonia and limbic encephalitis era target mature Shaker-type K+ channels: subunit specificity correlates with clinical manifestations. Brain 2006; 129:1570-1584.
Lai M. Hughes E, Peng X, Zhou L, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Annals of Neurology 2009; 65:424-434.
Lancaster E, Lai M, Peng X, Hughes E, et al. Antibodies to the GABAB receptor in limbic encephalitis with seizures: case series and characterization of the antigen. The Lancet Neurology 2009; 9:67-76.
Lancaster E, Martinez-Hernandez D, Dalmau J. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. Neurology 2011; 77: 179-189.
Lizuka T, Yoshi S, Kan S, et al. Reversible brain atrophy in anti-NMDA receptor encephalitis. Journal of Neurology 2010; 257:1686-1691.
Machodo S, Pinto A, Irani S. What you should know about limbic encephalitis. Arquivos de neuro-psiquiatria 2012; 70:817-822.
Masopust J. Andrys C, Bazant J, et al. Anti-NMDA receptor antibodies in patients with a first episode of schizophrenia. Neuropsychiatric Disease and Treatment 2015; 11: 619-623.
Moscato E, Jain A, Peng XHughes E, Dalmau J, Balice-Gordon R. Mechanisms underlying autoimmune synaptic encephalitis leading to disorders of memory, behavior and cognition: insights from molecular, cellular and synaptic studies. Eur J Neurosci. 2010; 32(2): 298-309.
Ojeda-Lopez C, Espinola-Nadurille M, Gonzalez-Aguilar A, et al. Anti-NMDAR encephalitis: an unrecognized aetiology in catatonic patients? 2015, P30, Delegate Program Booklet. The Lancet Neurology, Autoimmune Disorders Conference, March 26-7, Barcelona, Spain.
Pillai S Gill D, Webster et al. Cortical hypometabolism demonstrated by PET in relapsing NMDA receptor encephalitis. Pediatric Neurology 2010; 43:217-220.
Ramanathan S, Mohammad S, Brilot F, Dale R. Autoimmune encephalitis. Journal of Clinical Neuroscience 2013 [Epub ahead of print].
Rosenfeld M, Titulaer M, Dalmau J. Paraneoplastic syndromes and autoimmune encephalitis. Neurology: Clinical Practice. September 2012; 215-223.

Tidswell J, Kleinig T, Ash D, Thomposon P, Galletly C. Early recognition of anti-N-methyl D-aspartate (NMDA) receptor encephalitis presenting as acute psychosis. Australasian Psychiatry 2013; 21: 596-599.
Tsutsui K, Kanbayashi T, Tanaka K, et al. Anti-NMDA-receptor antibody detected in encephalitis, schizophrenia, and narcolepsy with psychotic features. 2012. Web.
Zandi M, Irani S, Lang B, et al. Disease-relevant autoantibodies in first episode schizophrenia. J Neurology 2011; 258:686-688.