Leading Article

Autoimmune encephalitis: An emerging entity

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Introduction

The importance of immunology in relation to neurological diseases has long been recognized. The first description of immune mediated encephalitis was in 1960’s by Corsellis et al and Brierley et al, who separately documented a form of encephalitis with poor prognosis in adults with tumours. The demonstration of anti-neuronal antibodies associated with this form of encephalitis (Hu, CV2/CRMP5, Ma2, amphiphysin, among others) in the mid1980s reinforced the concept of immune mediated encephalitis.

The last decade has seen the discovery of another group of antibodies associated with encephalitis. These target the central nervous system cell surface receptors and intracellular proteins that are involved in synaptic transmission, plasticity and neuronal excitability [Antibodies to components of voltage-gated potassium channel complexes (VGKCs), NMDA receptors (NMDARs), AMPA receptors (AMPARs), GABA type B receptors (GABABRs) and glycine receptors (GlyRs)]. The excitement around the discovery is mainly due to the eminent treatability of this condition. This form of encephalitis is seen in the paediatric group and appears to be severe in many and in some even fatal. Furthermore, many children seem to be exhibiting clinically recognizable syndromes which aid early recognition and enable successful treatment with disease modifying agents. This new group of antibodies is often not associated with neoplasms, especially in the paediatric patients. The two commonly found autoantibodies are those directed at the components of VGKCs and NMDARs.

A recent report from the United Kingdom highlights that, of the children suspected to have autoimmune encephalitis antibodies were identified only in 50%. Notably the antibody positive as well as negative patients showed equally impressive responses to immune modulatory therapy. This is likely to be a pointer to antibodies yet to be identified and has led to the suggestion that empirical therapy should be offered to children with suspected autoimmune encephalitis even in the absence of a positive antibody test.

The clinical syndromes associated with these antibodies are not restricted to encephalitis. New onset seizures, typically temporal lobe seizures and refractory status, with or without fever are described. A pure psychiatric presentation of acute or subacute (less than 12 weeks) onset is also possible. Other described clinical phenomena identified to be associated with anti-neuronal antibodies are cerebellar ataxia, progressive encephalomyelitis with rigidity and myoclonus and Morvan syndrome (neuromyotonia with autonomic dysfunction, insomnia and psychosis). A host of other conditions affecting the nervous system are suspected to be of autoimmune origin and two well known examples are opsoclonus myoclonus syndrome and Sydenham chorea. An active search for previously unidentified neuronal antibodies or other mechanisms in these conditions are ongoing in several centres in the world.

This article will concentrate on the highly treatment responsive encephalitic forms of illness resulting from the latter group of antibodies, namely antibodies to VGKCs and NMDARs.

The disease burden

The identification of aetiologies for encephalitis continues to be challenging even in the 21st century. A systematic review in 2010 found that the aetiology was not identified after extensive
investigations in more than 50% across the 41 studies reviewed. Further of note is that a study of a large cohort of over 1500 patients presenting with encephalitis in California, showed that only 16% had a confirmed aetiologi- cal agent. This highlights the potential importance of an immune mediated causation in encephalitis.

A multicentre study of 203 patients in the United Kingdom (UK) in 2010 demonstrated that 9% of encephalitis was antibody mediated. In the California encephalitis project the frequency of anti-NMDA receptor encephalitis surpassed that of any individual viral encephalitis in persons less than 30 years of age. This disorder is found to be increasingly common among children, who comprise up to 40% of all cases of antibody mediated encephalitis.

The prevalence in children with a severe form of encephalitis seems to be even higher. A Taiwan group studying 34 consecutive paediatric patients with severe encephalitis found autoantibodies in close to 50%. In the California encephalitis project, intubation rates were significantly higher for anti-NMDAR cases (41%) than for cases with other aetiologies. In UK, the worst outcome following encephalitis was found in those with antibody mediated encephalitis.

Clinical features

The clinical features are largely dependent on the antibody and the area of brain involvement. The presentation may be that of limbic encephalitis or multiphasic encephalitis with limbic and extra limbic involvement. Although a clinically recognizable syndrome is seen in many patients, differentiation from acute viral encephalitis may be difficult in some instances, especially in those presenting with a severe neurological syndrome.

Limbic encephalitis

The clinical features, classically associated with antibody mediated encephalitis, is related to dysfunction of the limbic system, which appears to be a prime antigenic target. The limbic system consists of cortical and sub cortical structures such as the amygdala, thalamus, hypothalamus and medial temporal lobes and is responsible for modulating behaviour, emotions, memory, autonomic and neuro-endocrine functions. The clinical presentation therefore is typically of behavioural disturbance, changes in personality and memory with cognitive impairment which may be associated with seizures. A frank schizophrenia like presentation may be seen. Misdiagnosis as a psychiatric disorder is not uncommon in this instance. Limbic encephalitis is commonly seen with VGKC-complex antibodies (LGI1, CASPR2, Contactin-2). A smaller proportion may show antibodies to NMDARs, GAD, AMPARs or GABABRs.

A characteristic feature of limbic encephalitis due to VGKC-complex antibodies is facio-brachial dystonic events (episodic arm and face dystonia) which might precede the cognitive involvement. These events rapidly respond to immunotherapy and treatment may prevent progression to limbic encephalitis.

### Limbic encephalitis (LE)

- Mostly seen with anti VGKC complex antibodies.
- Classical clinical features are changes in cognition, behavior and personality associated with seizures.
- Facio-brachial dystonic events are a hallmark early feature of anti VGKC complex antibody mediated LE.

### Multiphasic cortico-subcortical encephalitis

Anti NMDA receptor disease is the commonest antibody mediated encephalitis in the paediatric age group. These antibodies could give rise to an isolated limbic encephalitis but is often associated with a diffuse encephalitis not restricted to the limbic system. Several extensive descriptions of the clinical features have been published, including a review of 400 patients with anti NMDAR antibodies in 2011.

The characteristic clinical syndrome evolves in several phases which may overlap.

**Prodromal phase:** This consists of a non specific flu like illness with fever and headache and may last for about 2 weeks. This may not be seen in all persons and is usually associated with an infection.

**Early phase:** The prodrome is followed within days by a phase characterized by psychiatric symptoms, sleep disturbances and seizures.
Late phase: Within days to weeks, the progression continues to the next stage where patient develops abnormal and involuntary movements, autonomic disturbances and oculomotor dysfunction. Impaired consciousness may be seen in the majority by this time. Headache and fever without infection could also be a feature in this stage.

**Description of clinical features**

The psychiatric features and seizures may be seen in both forms of encephalitis while the other features described are seen in NMDAR antibody related more diffuse multiphasic encephalitis.

**Psychiatric symptoms**

A variety of psychiatric symptoms may be seen in antibody mediated encephalitis. An acute or subacute onset is usual. Seventy-seven of 100 anti-NMDA receptor encephalitis cases reported by Dalmau et al developed marked schizophrenia-like psychiatric symptoms at onset. There may be associated, features such as catatonia, visual and auditory hallucination, short term memory disturbance and grandiose or hyper religious delusions. A prolonged catatonic phase with long periods of reduced movements, where the child is quite still and akinetic, punctuated by periods of agitation or delirium, which can be extreme at times, is characteristic. The periods of agitation may be so severe as to compromise patient safety and could necessitate sedation.

Children are likely to show diminished or paradoxical response to stimuli demonstrated by elective dysfunction such as refusal to swallow. Mutism is quite common. The elective nature of the speech dysfunction is seen by careful observation where the child would talk in sleep or at unguarded times. Similarly the child may appear to be unable to swallow any liquid or solid placed in the mouth while not having any drooling of saliva which would be seen in an actual severe swallowing dysfunction. Echolalia (word repetition) and coprolalia (use of socially unaccepted language) may be seen in some. Other hallmark features include poor eye contact and absent or inconsistent visual tracking and emotional lability.

At times mild psychiatric conditions such as new onset temper tantrums, changes in the mood or personality may be the presenting feature.

**Sleep disturbances**

Virtually all patients develop variant sleep pattern including reversal of day night cycle, insomnia and hypersonmia. Hypersonmia is reported as an early feature, while insomnia occurred later in a series from UK.

**Involuntary movements**

Involuntary and abnormal movements are seen in the majority with oro-facial dyskinesia being considered the hallmark movement. These include grimacing, chewing-like movements and repetitive jaw opening and closing and licking resulting in lip, tongue and teeth injuries at times. Abnormal limb and body movements consist of bizarre and dystonic posturing, choreiform movements as well as stereotypies (repetitive, non-functional or harmful movements). Common examples are repetitive hair pulling or head rubbing. These involuntary movements, especially the oro-facial dyskinesia, in the setting of a critically ill and ventilated patient may be the most obvious clinical clue to the diagnosis.

**Autonomic symptoms**

Autonomic instability is very common in anti-NMDAR encephalitis and is reported to be seen in 70-90% 9,10,12,17,18. This may contribute to mortality and includes instability of blood pressure, hyper salivation, hypoventilation, hyperhidrosis, hyperthermia and pseudo obstruction. Cardiac dysautonomia, including brady and tachy arrhythmias as well as asystole 12, necessitates pacemaker insertion in up to 4% of adults 9. Severe cardiac dysrhythmias are uncommon in children 10,17. Central hypoventilation, which affects more adults than children, remains a significant problem and is reported to affect 23% children with NMDAR antibodies in report by Florence et al 10.

**Seizures**

Seizures are a common feature and may vary in frequency and intensity from complex partial seizures to refractory status epilepticus. Response to antiepileptic medications is usually poor.

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<thead>
<tr>
<th>Multiphasic cortical- subcortical encephalitis with NMDAR antibodies</th>
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<td><strong>Three phases of evolution:</strong></td>
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<tr>
<td>• Prodrome: Non-specific flu like illness with fever and headache</td>
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<tr>
<td>• Early phase: Psychiatric symptoms, sleep disturbances and seizures</td>
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<td>• Late phase: Involuntary movements, autonomic disturbances, oculomotor dysfunction, impaired consciousness</td>
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**Characteristic clinical features:**

- Psychiatric symptoms
- Seizures
- Altered consciousness
- Sleep disturbances
- Involuntary movements
- Autonomic symptoms
- Ocular motor phenomena
**Hyponatraemia**

Hyponatraemia has been increasingly recorded as an association of some forms of autoimmune encephalitis. The recently described anti-LGI1-associated encephalitis is complicated by severe and life threatening hyponatraemia in up to 60% of cases. The exact cause of hyponatraemia is unclear. LGI1 is strongly expressed in the hypothalamus in animal models, and is also expressed in specific tubules of the kidney. Hyponatraemia may therefore be due to effect on hypothalamic antidiuretic hormone production or renal tubular sodium transport.

**Association with neoplasms**

In children, the presence of an underlying tumour is seen much less commonly than in adults. The commonest tumour in females is ovarian teratoma. Others include thymomas, breast and lung cancers. Varying rates of tumour presence at diagnosis of NMDAR encephalitis have been recorded. Dalmau et al reports this to be about 25%9,10,12,13. Other observations include nystagmus and abnormal ocular position both in the vertical and horizontal axis. Inverse oculor bobbing which is a slow downward eye drift followed by fast return to mid position, is also described14.

**Diagnosis**

The diagnosis is by recognition of the clinical features and demonstration of the antibody in the CSF or serum. This is complicated by the absence of classical clinical features in some with demonstrated antibodies and vice versa by the absence of demonstrable antibodies in those with the immune modulatory therapy responsive classical clinical syndrome. Detection of Herpes virus antigens and serum Mycoplasma IgM antibodies are concomitantly with anti NMDAR antibodies in several children with encephalitis has further complicated the scenario.15 Again, low titres of antibodies could be found in those with unrelated conditions. Exclusion of other aetiology is important especially when antibody testing is not available. Findings that may help with the diagnosis include cerebrospinal fluid (CSF) examination, electroencephalogram (EEG) and imaging. A response to immunotherapy is also considered of diagnostic value. Recent review by Ziliani et al has suggested criteria for recognition in those without the classical clinical features and recognized antibodies.

**Cerebrospinal fluid**

The CSF is abnormal in the majority of the cases, showing lymphocytic pleocytosis and less frequently increased protein or oligoclonal bands. The reactive changes are more likely to be seen in the early stages of the illness though positive oligoclonal bands are more likely during the late stage. CSF changes are unusual in limbic encephalitis with VGKC antibodies.

**Electroencephalogram (EEG)**

The EEG is abnormal in the vast majority. The common pattern is slowing which may be diffuse or focal. A recent study identified a unique EEG pattern, called “extreme delta brush” which is beta-delta complexes, in adults with anti-NMDAR encephalitis. Epileptiform activity is less common than slowing, but may include electrographic seizures in approximately 60% when continuous monitoring is undertaken. The epileptiform activity may be seen only in the early stages, and may even deteriorate to a non convulsive status. Localization of the epileptiform activity is commonly temporal or at times frontal.

**Imaging**

Computed tomography (CT) is usually normal as is early magnetic resonance imaging (MRI). MRI changes may be seen later in some but not all cases with T2 and fluid-attenuated inversion recovery (FLAIR) sequences appearing abnormal. The changes are non specific and may be cortical or subcortical. Changes restricted to the temporal lobe or limbic system, are the commonest findings in patients with limbic encephalitis. Abnormalities reported with more diffuse encephalitis have been in the periventricular white matter, limbic or temporal lobes, brainstem, basal ganglia and cerebellum. Meningeal enhancement has also been found occasionally. Functional imaging, especially positron emission tomography (PET) may be abnormal in some with normal MRI.
Treatment and outcome

Disease modifying therapy

The standard treatment is with pharmacological immunosuppressive therapy. Plasmapheresis is also reported to be helpful. A thorough search for a tumour followed by removal appears to be essential. Corticosteroids are the commonest agents used and intravenous immunoglobulin (IVIG) and/or plasmapheresis is routinely combined with this by many. Combined therapy appears to increase remission rates. Steroids are usually started at high doses (e.g. methyl prednisolone 30 mg/kg intravenously daily for 3 to 5 days) and slowly tapered. In case of poor response combination therapy or longer courses of high dose steroids may be used though as mentioned earlier, some centres routinely employ combination with IVIG or plasmapheresis. There are no definitive guidelines regarding duration (or dose) of therapy though weeks or months of immunosuppressive therapy is commonly employed. Short treatment courses could result in a relapse of symptoms. When available, antibody titres are a good guide to therapy.

Some patients, especially those with NMDAR antibodies, need more than 3 immunosuppressive agents for optimal response. The agents reported to have been used with good results are cyclophosphamide, mycophenolate mofetil and rituximab. Rituximab is increasingly favoured due to the response and side effect profile. A good initial response can be expected in some though relapses are not uncommon. Early immunosuppressive therapy and prompt tumour removal appears to favourably affect the outcome. Even when treated, deficits and even death may not be avoidable in some. The residual deficits are fortunately mild in the majority and clinical improvements may continue for as long as two years. Occasional patients have recovered without immunotherapy.

Tumour surveillance

Active surveillance for a tumour is indicated in all children suspected to have autoimmune encephalitis especially if anti NMDAR antibodies are demonstrated or thought to be the cause. Imaging, ideally MRI of the chest and abdomen are usually used. There is no clear recommendation regarding how hard one should be looking for a tumour or regarding the need for long term surveillance. A thorough search for a neoplasm is certainly important in those who do not respond or respond poorly to therapy.

Supportive Therapy

Supportive therapy has a major impact on the disease outcome. Many children would need intensive care. Special attention should be focused on constant vigilance for autonomic dysfunction and intervention when necessary. Hyponatraemia, when present, needs careful attention as this can contribute to mortality. Seizures, involuntary movements and psychiatric manifestations can be extremely difficult to handle and appear to resist usual treatment. The help of an experienced psychiatrist is essential in the management of many of these children. All the above manifestations appear to show best response to immunosuppressive therapy.

Components in treatment of autoimmune encephalitis

- Immunotherapy: Initially with high dose steroids combined with IVIG and/or plasmapheresis. One or more other agents such as Rituximab may be needed. Long duration of therapy is indicated in many for optimal response and to prevent relapse.
- Tumour removal is an integral component
- Supportive therapy with special attention to hyponatraemia and autonomic dysfunction is crucial.
- Multidisciplinary care including psychiatric expertise and rehabilitative support is needed.
Many children need rehabilitative care and nutritional support for optimal recovery.

Summary
A novel group of anti-neuronal antibodies giving rise to various neurological diseases have been identified. The resultant clinical syndromes have some characteristic clinical features which enable early recognition. Children appear to be especially vulnerable to encephalitis caused by these antibodies. Antibody testing is available commercially in many countries including Sri Lanka. The treatable nature of these conditions has promoted a massive wave of interest and more and more cases are reported worldwide. Early treatment is shown to alter the disease course. The first line treatment is steroids combined with IVIG and/or plasmapheresis with removal of any identified tumour. More immunosuppressants may be necessary in some. There are no firm guidelines regarding treatment doses and durations though months of treatment are needed in many. The association with tumours is not strong but screening for tumours is recommended. Majority have near complete recovery though relapses are not uncommon.

References


24 Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology* 2012; **79**:1094-100. [http://dx.doi.org/10.1212/WNL.0b013e3182698c08](http://dx.doi.org/10.1212/WNL.0b013e3182698c08)


