Introduction

Encephalitis (brain inflammation) is often thought to be mediated by infections (e.g. viral). With the advances in molecular diagnostics, new immunological markers (antibodies) are being discovered in patients presenting with encephalitic syndromes. Thus, research has evoked interest in the ‘immune theory’ of encephalitis. This group of disorders is appealing to clinicians because of the favourable response to immunotherapy viz a viz infectious encephalitis where limited pharmacotherapy is available for most of the viral agents.

Various syndromes of autoimmune encephalitis have been described and many more are expected with the advent of newer biomarkers. The clinical syndrome comprises a complex of encephalopathy, cognitive disturbances, mood/personality changes, seizures and movement disorders. Each of these can be the presenting manifestation, opening up a wide differential diagnosis, often delaying the diagnosis and therapy. The purpose of this review is to update recent information on autoimmune encephalitis.

Table 1: Clues for diagnosis of autoimmune encephalitis

- Subacute onset of memory impairment (short-term memory loss), encephalopathy or psychiatric symptoms
- At least 1 of the following:
  - Focal neurological deficits
  - Unexplained seizures
  - CSF pleocytosis (white blood cell count >5 cells per mm3)
  - MRI features suggestive of encephalitis.
- Exclusion of alternative causes

This may be supplemented by T2 hyperintensity on MRI (most commonly in the mesial temporal region), inflammation in CSF, hypometabolism on functional imaging and confirmation comes with detection of specific autoantibody. (Improvement after immunotherapy may be diagnostically informative). However, obtaining autoantibodies...
Table 2: Diagnostic clues: anti-NMDA receptor encephalitis

1. Rapidly progressive following symptoms:
   - Abnormal behaviour or cognitive dysfunction
   - Decreased level of consciousness
   - Speech dysfunction
   - Seizures
   - Movement disorder, especially oral dyskinesias
   - Autonomic dysfunction or central hypoventilation
2. At least one of the following study results:
   - Abnormal EEG (slowing, epileptiform activity or extreme delta brush)
   - CSF pleocytosis or oligoclonal bands
3. Exclusion of other disorders
4. Accompanied by a systemic teratoma
5. IgG anti-GluN1 antibodies (Definite)

Well Characterized Autoimmune Encephalitis Syndromes

Anti-NMDAR-encephalitis

Anti-NMDAR-encephalitis is the most common autoimmune encephalitis in which IgG antibodies against the GluN1 subunit of the NMDA receptor are present. It can affect all age groups, but is more common in children and young adults females.

The clinical presentation can be divided into following stages.

1. Prodromal phase with infection; fever and headache
2. Early stage with psychosis, confusion, amnesia and dysphasia
3. Late stage (within 1–2 weeks) characterised by movement disorders (choreo-athetoid movements, stereotypy), autonomic instability, encephalopathy with hypoventilation. Some patients become mute and catatonic.

Other clinical presentations are

1. Autoimmune refractory epilepsy
2. Schizophrenia like symptoms
3. Demyelinating disorder
4. Patient with herpes simplex encephalitis with anti NMDA receptor antibodies

Tumours are present in 40-50% in women older than 18 years. Most common tumour is ovarian teratoma. Other types of malignancies (small-cell lung, pancreatic, and breast cancer and Hodgkin’s lymphoma) have occasionally been identified. Some patients do not have an underlying neoplastic disease. Nevertheless, all patients should undergo extensive tumour screening, at presentation and at yearly intervals. Better outcomes have been reported with early resection of tumour.

MRI brain is often normal. If abnormalities are present, they are seen as T2, FLAIR hyperintense lesion either in limbic cortex, in the brainstem, basal ganglia or the cerebellum. Moderate lymphocytic pleocytosis can be seen in CSF. NMDA receptor antibodies are synthesized both systemically and intrathecally. Up to 15% of patients do not have serum antibodies, but do have positive CSF antibodies. EEG shows widespread theta-delta activity suggestive of diffuse cerebral dysfunction. Also a particular pattern is observed; extreme delta brush (slow waves with overriding fast beta activity) in 30% of patients. Detection of this unique pattern should prompt consideration of anti NMDA receptor encephalitis. Their presence also suggests a more prolonged disease course.

About 50% patients treated with first line immunotherapy using steroids, intravenous immunoglobulins, plasmapheresis and tumour removal show improvement within 3-4 weeks. Patients who do not show improvement to first line therapy can potentially show good response to second line immunotherapy like rituximab, cyclophosphamide and others. Some experts recommend comprehensive immunotherapy that consists of giving rituximab, lVig or PE and methylprednisolone up front, all at the same time to alter the natural course of disease and to prevent relapse.

Case Vignette: 17 year female presented with abnormal fluctuating behaviour (paranoid ideation) and focal seizures over 6 weeks. After 1-2 weeks, she developed abnormal posturing of the right hand with involuntary perioral movements, refractory status epilepticus and mutism. There was no history of...
fever, headache, myoclonic jerks, visual complaints, weight loss or any systemic complaints. At the time of admission, she was in encephalopathy with status epilepticus, and had pyramidal signs with right upper limb dystonic posturing and perioral dyskinetic movements. During hospital stay, she developed autonomic disturbances, respiratory distress for which she was intubated and mechanically ventilated.

Routine investigations including anti TPO antibody level were within normal limits. MRI brain and CSF studies were also normal. Her EEG showed generalised theta-delta range slowing with “delta brush” and focal epileptiform discharges as well (Figure 2). CSF anti-NMDA receptor antibody was positive.

She received a course of intravenous methylprednisolone (MPS) followed by intravenous immunoglobulin’s (IvIg) but showed no signs of improvement. Later on, weekly regime of rituximab (375mg/m²) was given. She improved significantly and subsequently weaned off the ventilator. Presently she is on low dosage of steroids and course of rituximab with regular monitoring of CD4⁺ levels.

**Learning Points**

- Young female presenting with psychiatric symptoms can have autoimmune encephalitis.
- Delta Brush on EEG is an important marker and should be looked for in every patient of suspected NMDA encephalitis.
- Rituximab can increase yield in non-responders.

**VGKC-Complex antibodies mediated encephalitis**

Diseases associated with VGKC complex antibodies include limbic encephalitis, epilepsy, neuromyotonia/peripheral nerve hyper excitability and Morvan’s syndrome. Limbic encephalitis is the most common syndrome form.¹³ The antibodies directed against proteins of the VGKC-complex include LGI1, CASPR2, and Contactin-2.¹³

**Anti LGI1 associated encephalitis**

Anti LGI1 encephalitis presents with memory loss, confusion, temporal lobe seizures, agitation, and other psychiatric features evolving over several days or weeks and predominantly affects elderly males. Some patients develop brief tonic or myoclonic-like seizures (also called facio-brachial dystonic seizures) that precede the memory and cognitive deficits.¹³ Low serum sodium concentrations have been reported in 60% patients.¹³ Rapid eye movement sleep behaviour disorder is common in these patients.¹⁴ MRI brain shows T2 and FLAIR hyper intensities in the mesial temporal lobes, but up to 40-50% of patients can have normal MRI.¹⁵ The CSF is usually normal, although mild inflammatory changes may be present. EEG usually shows inter-ictal epileptiform activity or slowing over anterior or mid-temporal region. Association with tumours is very rare. Majority of patients respond well to immunotherapies such as steroids, plasma exchange, and Ivlg. These patients tend to have a monophasic disease, but 20% patients relapse.¹⁵

**Case Vignette: A 59 year old Doctor was admitted with**

frequent left upper limb and facial jerky involuntary movements with fluctuating encephalopathy. During hospital stay frequency of jerks increased to every 2-3 minutes. He was afebrile and his routine haematological and biochemical investigations and CSF studies were normal. MRI brain was suggestive of T2 and FLAIR hyperintense signal in bilateral mesial temporal lobe (Figure 3). EEG showed diffuse generalised intermittent slowing (Figure 4). His anti-VGKC antibody- anti LGI1 was strongly positive. He was given valproate, clonazepam and methylprednisolone [MPS] course.
was added with short course of steroid sparing immunomodulator there was recurrence of symptoms, with worsening of sensorium. Since his facio-brachial jerks increased while tapering steroids and AEDs, reduction in jerks and confusion.

Learning Points

- Fasciobrachial jerks predominate and are early in clinical presentation.
- Some patients of LGI1 R encephalitis may relapse and requires second line immunosuppression.

Anti-CASPR2 Associated Encephalitis

Patients with CASPR2 antibodies usually develop Morvan’s syndrome. This syndrome was first described in 1890 by Augustin Morvan as a syndrome associated with autonomic dysfunction and severe insomnia. Patients with Morvan’s syndrome present with a subacute onset of peripheral nerve hyperexcitability (PNH), dysautonomia, and encephalopathy with marked insomnia.

More than half of patients complain of pain, which could be of a neuropathic nature or manifest as arthritis or myalgia. Dysautonomia leads to variable hyperhidrosis, cardiac arrhythmias, haemodynamic disturbances, impotence, constipation, urinary problems, excess salivation, and lacrimation. Rare cases of isolated limbic encephalitis or PNH have been reported. Patients may have other coexisting immune mediated disorders such as myasthenia gravis with antiacetylcholine (AChR) or muscle-specific kinase (MuSK) antibodies. A high proportion of the VGKC-complex antibodies in Morvan’s syndrome are directed against CASPR2, but some patients have LGI1 antibodies. MRI brain is often normal. Thymoma is most common tumour associated with Morvan’s syndrome. Some patients recover spontaneously, but majority of patients show good response to immunotherapy.

Case Vignette: An 18 years old boy was admitted with 4 weeks history of bilateral lower limb cramps, insomnia and flickering muscle movements over all 4 limbs even in sleep. Examination showed postural drop in blood pressure with myokymia in all 4 limbs and tremors of bilateral hand with involuntary movements of toes. EMG showed myokymia (Figure 5) with normal NCS. MRI showed myokymia (Figure 5) with normal NCS. MRI, EEG and CSF study were normal. His anti VGKC antibody (CASPR 2) was strongly positive, confirming the diagnosis of Morvan’s syndrome. There was no evidence of malignancy on PET CT. He was given iv MPS for 5 days followed by oral steroid and carbamazepine for myokymia. His cramps and sleep improved within few days with significant reduction in myokymia.

Learning Points

- Patients can present with lower motor neurone features like cramps, neuromyotonia, insomnia, autonomic dysfunction without encephalopathy.
- Malignancy is seen in only a proportion of patients.
- Hashimoto’s encephalopathy

Hashimoto’s encephalopathy is a steroid responsive encephalopathy characterized by fluctuating or persisting altered sensorium and neurologic deficits associated with elevated blood concentrations of anti-thyroid antibodies. Antibodies associated with this condition include antithyroid peroxidase antibodies (antithyroid microsomal antibodies) and antithyroglobulin antibodies. Based on the consistent and spectacular steroid response, the condition has been renamed as steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT). The clinical presentation is of fluctuating or progressive encephalopathy, myoclonic jerks, seizures, stroke like episodes. It is important to bear in mind that the thyroid-stimulating hormone levels can be normal in this disorder. CSF often shows elevated protein levels without pleocytosis. EEG is usually abnormal showing generalized slowing. Triphasic waves, focal slowing, and epileptiform abnormalities may also be seen. MRI of the brain is often normal in 50% of cases, but can reveal subcortical white matter hyperintensities on T2-weighted or fluid-attenuated inversion recovery (FLAIR) imaging and brain atrophy. Treatment includes high dose steroids. The neurological and psychiatric symptoms respond early to treatment, although EEG normalization takes some

Learning Points

- Encephalopathy with seizures, myoclonus, hallucinations, or stroke-like episodes
- Subclinical or mild overt thyroid disease (usually hypothyroidism)
- Brain MRI normal or with non-specific abnormalities
- Presence of serum thyroid (thyroid peroxidase, thyroglobulin) antibodies
- Absence of well characterised neuronal antibodies in serum and CSF
- Exclusion of alternative causes

Table 3: Clues for Diagnosis of Hashimoto’s encephalopathy

<table>
<thead>
<tr>
<th>Clue</th>
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<tr>
<td>Encephalopathy with seizures, myoclonus, hallucinations, or stroke-like episodes</td>
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<td>Exclusion of alternative causes</td>
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time. Around 2-5% of patients may not respond to steroids, in whom azathioprine, IVlg or plasmapheresis can be used with good results. Table 3 lists the clues to the diagnosis.

Case Vignette: 65 year old female presented with altered behavior since 1 month. Relatives noticed that she was not recognizing close relatives, and had fluctuating mutism and sphincter incontinence, visual hallucinations. On examination she was disoriented with poor attention span. She was moving all 4 limbs and all reflexes were brisk. Hemogram and routine biochemical tests including electrolytes were normal. Erythrocyte sedimentation rate was 60mm at 1 hr with normal serum ammonia level. T3 - 66.5 ng/dl [N=70-204], T4- 3.77 microG/dl [N=4.83-11.72], TSH – 7.82. Anti- TPO antibody titre- > 1000 IU/ML. CSF study was normal. EEG showed intermittent generalized slowing and MRI brain was suggestive of bilateral white matter T2/FLAIR hyperintense signal (Figure 6). She was treated with inj MPS 1gm iv for 5 days followed by oral steroid taper and levothyroxine replacement. She responded dramatically to treatment and was cognitively normal within a week.

Learning Points
- In elderly patients with altered sensorium, one should consider Hashimoto’s encephalopathy after excluding alternative causes, even in absence of myoclonic jerks.
- Patients show dramatic response to steroids.

**Anti-GABA Receptor Encephalitis**

**Anti-GABA-B Receptor Encephalitis**

Anti-gamma-aminobutyric acid B receptor (GABA-B R) encephalitis affects men and women similarly and present with the typical features of limbic encephalitis and prominent seizures. They frequently have underlying small cell lung carcinoma. Cerebellar ataxia and opsoclonus–myoclonus syndrome can co exist. The brain MRI is often abnormal showing unilateral or bilateral medial temporal lobe FLAIR/T2 signal consistent with limbic encephalitis and CSF can show lymphocytic pleocytosis.

**Anti-GABA-A Receptor Encephalitis**

Patient present with refractory seizures and status epileptics. It is preceded by rapidly progressive, severe encephalopathy. Majority of patients have extensive MRI abnormalities on FLAIR and T2 imaging with multifocal cortical-subcortical involvement without contrast enhancement. No cancer association has been seen.

**Anti-AMPA Receptor Encephalitis**

Anti AMPA-R encephalitis predominantly affects middle-aged women (median age 60 years) and patients present with subacute onset symptoms of limbic encephalitis associated with prominent psychiatric symptoms. Patients with anti-AMPA-R-antibody associated limbic encephalitis have a high...
Algorithm 1: Clinical approach to autoimmune encephalitits

tendency to relapse.\textsuperscript{31} About 70% have an underlying tumor in the lung, breast, or thymus.\textsuperscript{32} AMPA-R encephalitis patients respond well to immunotherapy and tumor treatment.

Disorders associated with GlyR antibodies

Anti-glyR antibody-related encephalitis patients presents with progressive encephalomyelitis with rigidity and myoclonus (PERM).\textsuperscript{33,34} They may also present with muscle stiffness, hyperactive startle responses and limb spasms.\textsuperscript{35} These cases are mostly unrelated to cancer and patients often have good responses to immunotherapy. Table 4 sumnerizes the salient features of this group of conditions.

Newer disorders

Anti-DPPX Encephalitis

The encephalitis associated with antibodies to dipeptidylpeptidase-like protein-6 (DPPX) was recently described, it predominantly affects adults (age 45–76 years). Patients present with prominent neuropsychiatric symptoms usually preceded by intense diarrhea.\textsuperscript{36} This syndrome is also characterized by trunk stiffness, hyperekplexia, marked cerebellar ataxia in few patients.\textsuperscript{37}

Encephalitis with Antibodies to IgLON5

This is recently described disorder with antibodies to IgLON family member 5 has a median age of onset of 59 years. Patients develop abnormal REM and non REM sleep movements, and behaviours and obstructive sleep

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Algorithm 1: Clinical approach to autoimmune encephalitits

Autoimmune encephalitis

Predominant neuropsychiatric features

(Behavioural; personality change, psychosis, confusion, confabulation, agitation)

Predominant neurological feature

Age of Onset

Young Age

Anti NMDA

autonomic dysfunction, stereotyped movements

Anti GABA R1

Epilepsy

Hallucination, epilepsy, coma

Old Age

Anti AMPA

Epilepsy, Ataxia.

Fasciobrachial dystonia

Cognitive decline with myoclonic jerks

Neuromyotonia with autonomic dysfunction and memory loss

encephalomyelitis with rigidity and myoclonus

Anti VGKC-CASPR2

Morvan’s syndrome

Anti Glycine R encephalitis

Anti VGKC-LGi 1

Hashimoto encephalitis

Brainstem encephalitis with autonomic dysfunction and memory loss

Anti NMDA

PALS

Anti AMPA

Epilepsy

Anti GABA R1

Epilepsy

Antibodies to dipeptidylpeptidase-like protein-6 (DPPX)

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Encephalitis with Antibodies to IgLON5

This is recently described disorder with antibodies to IgLON family member 5 has a median age of onset of 59 years. Patients develop abnormal REM and non REM sleep movements, and behaviours and obstructive sleep
apnea. Brain MRI, EEG, and CSF studies and electromyography is often normal. Patients usually have a rapidly progressive course with poor response to immunotherapy. Death can occur due to autonomic dysfunction.

**Anti mGluR5**

Patients with antibodies to the metabotropic glutamate receptor 5 have been reported to present with cerebellar ataxia, limbic encephalitis. The co-occurrence of limbic encephalitis and Hodgkin lymphoma is known as Ophelia syndrome.

Algorithm 1 and 2 summarize the clinical and management aspects of immune encephalitis.

**Concluding Remarks**

As seen from the above discussion, immune mediated encephalitic syndromes form an important group of modifiable neurological disorders. These are being increasingly recognised due to availability of serum makers and have been better characterised in the recent years. These disorders have various patterns of clinical presentations which correlate with antibodies. Clinical suspicion and knowledge of these syndromes is vital.

**Diagnosis (refer table no 1.)**

**MRI brain** - UL/BL Mesial temporal hyperintensities or subcortical hyperintensity with or without enhancement.

**EEG** - Generalised or focal slowing and/or epileptiform discharges.

**CSF** - Elevated protein, pleocytosis, abnormal oligoclonal bands.

**Antibody testing**

**Acute Treatment**

IV MPS (1 gm daily for 5 days)

OR

IV Ig (0.4mg/kg daily for 5 days)

OR

Plasma exchange (severe attack, incomplete response to steroids)

**Algorithm 2: Management of autoimmune encephalitis**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>No Improvement</td>
<td>IV rituximab (375mg/m² weekly for 4 weeks) OR IV cyclophosphamide 1gm iv monthly for 6 months</td>
</tr>
<tr>
<td>Improvement</td>
<td>Maintenance treatment</td>
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<tr>
<td></td>
<td>Oral prednisolone taper over 4-6 months and consider</td>
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<tr>
<td></td>
<td>Oral azathioprine OR Oral mycophenolate mofetil OR IV rituximab (Monitor with CD 19 level)</td>
</tr>
<tr>
<td></td>
<td>IV cyclophosphamide 1gm iv monthly for 6 months</td>
</tr>
</tbody>
</table>

**References**


important to the clinician as these are amenable to immunotherapy.

References


