

Review Articles

Emergence of A New Entity: The Autoimmune Encephalitis

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Abstract:

Encephalitis has been known as a distinct entity for a long time but its exact cause has remained undetected in about half the cases in spite of extensive investigations. During the last few years there has been reports of cases of encephalitis in which antibodies has been detected against deep grey matter neurons. Antibodies have been detected against the N-methyl-D-aspartate (NMDA) receptors or voltage-gated potassium channels (VGKC). VGKC antibody positive encephalitis usually presents in middle aged or elderly people and is twice as common in men. The main symptoms are memory loss and seizures. Cognitive impairment, confusion, disorientation, personality change and behavioral disturbances are also common. Encephalitis associated with NMDA receptor antibodies is mainly seen in children and young adults, with women being affected about three to four times more often than men. Initially there is a period of cognitive impairment and psychiatric features like hallucinations, agitation and depression but later there is gradual deterioration in conscious level with autonomic features often requiring intensive care. The most striking feature of both these types of encephalitis is their uniform good response to immunomodulating therapies. Intravenous immunoglobulin (IVIG), glucocorticosteroids, plasma exchange and drugs like cyclophosphamide, rituximab, mycophenolate mofetil, azathioprine, singly or in combination have all produced good results. It is this surprisingly easily available effective treatment which makes diagnosis of this condition imperative. Encephalitis is a condition which is encountered by physicians at all levels and so a high level of awareness about the condition will ensure that the condition is not missed. This review about this new condition is being presented to make physicians aware about this devastating but easily treatable disease.

Keyword: Autoimmune encephalitis, auto antibodies, IUIG

Introduction:

With the development of modern medical science, diagnosis of various neurological disease is becoming easier day by day. Now-a days we neurologists do have answers to many disease that were not know to us. In a country like Bangladesh diseases like encephalitis require extra attention as many diagnoses are missed and have missed opportunity for timely treatment. That it's the purpose of this review.

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Encephalitis Lethargica:

Encephalitis refers to an acute, usually diffuse, inflammatory process affecting the brain parenchyma and the term is derived from the Greek *enkephalon*, meaning brain. It has been known for many centuries and has been described by physicians such as Hippocrates and Sydenham. The most recent devastating epidemic of Encephalitis occurred in the early 20th century (between 1916 and 1927) that killed an estimated 500,000 people worldwide.¹ Von Economo provided the most detailed description of the disease and termed it as Encephalitis lethargica.² There have been no further epidemics of EL since the 1920s, although sporadic cases have continued to be reported.^{3,4,5,6}

Limbic Encephalitis

The term limbic encephalitis was originally coined by Corsellis et al,⁷ and refers to the subacute onset of episodic memory impairment, disorientation and agitation, commonly associated with seizures, hallucinations, sleep disturbance and histological evidence of medial temporal lobe inflammation.⁸ Signal changes in the medial temporal lobes or hippocampi are frequently found on MRI. Limbic encephalitis is usually considered to be paraneoplastic in origin, and many reported cases are associated with specific

autoantibodies; mainly to Hu in patients with lung cancer,^{9,10,11} to Ma2 in patients with testicular tumours,^{12,13,14} or to CRMP5/CV2 in patients with thymomas.¹⁵

Encephalitis can be caused directly by a range of viruses, the herpes viruses and some arboviruses being especially important. Other microorganisms can also cause encephalitis, particularly protozoa such as *Toxoplasma gondii*, and bacteria such as *Listeria monocytogenes* and *Mycobacterium tuberculosis*. Encephalitis can also occur as an immune-mediated phenomenon—for example, acute disseminated encephalomyelitis (ADEM), which follows infections or vaccinations and paraneoplastic limbic encephalitis (PLE) associated with specific autoantibodies in patients with tumours. However, the finding of CSF oligoclonal bands (OCB)^{16,17,18} and the successful treatment of some recent cases with steroids⁵ had led investigators to propose that there may be an immune-mediated type of encephalitis also.

Limbic Encephalitis with antineuronal antibodies

As early as in 1999, Caselli et al¹⁹ reported about five patients, age 54 to 80 years, who presented between 3 weeks and 18 months after symptomatic onset of progressive cognitive decline, psychosis, and unsteady gait that proved to be due to a steroid-responsive nonvasculitic autoimmune inflammatory meningoencephalitic syndrome. CSF examination showed elevated immunoglobulin IgG index and increased IgG synthesis rate in all three patients in whom it was checked, and brain biopsy revealed perivascular lymphocytic infiltrates without vessel wall invasion.

In 2000, Gultekin et al,¹³ reported 50 patients with diagnosis of PLE and found that 30 (60%) patients had antineuronal antibodies (18 anti-Hu, 10 anti-Ta, 2 anti-Ma), and 20 were antibody-negative or had uncharacterized antibodies ($n = 4$). Immunotherapy improved 64% of patients without these antibodies.

Limbic Encephalitis with antibodies to voltage-gated potassium channels (VGKC)

In 2001, Buckley et al²⁰ reported two patients with symptoms of limbic encephalitis (LE), negative for typical paraneoplastic antibodies, in whom antibodies to voltage-gated potassium channels (VGKC) were detected retrospectively in serial serum samples. Plasma exchange was effective in reducing VGKC antibody levels, with substantial improvement in mental symptoms in one patient. Later other authors also reported patients with features suggestive of LE, who had no markers of paraneoplastic syndrome but had presence of voltage gated potassium channel antibodies (VGKC-Abs).²¹ Pozo-Rosich et al²² in 2003 reported 15 cases of limbic

encephalitis in four of which there was raised VGKC-Abs, with the two highest levels, >400 pM (neurological and healthy controls <100 pM) associated with non-paraneoplastic disorders and remission following immunosuppressive treatment.

Vincent et al²³ in 2004 reported 10 patients with histories of memory loss, confusion and seizures. Paraneoplastic antibodies were negative, but VGKC-Ab ranged from 450 to 5128 pM (neurological and healthy controls <100 pM). Variable regimes of steroids, plasma exchange and intravenous immunoglobulin were associated with variable falls in serum VGKC-Abs, to values between 2 and 88% of the initial values, together with marked improvement of neuropsychological functioning in six patients, slight improvement in three and none in one. The improvement in neuropsychological functioning in seven patients correlated broadly with the fall in antibodies.

There were also reports of patients with raised VGKC antibodies presenting with other syndromes like fronto-temporal dementia and elevated VGKC-Ab titer (2624 pM), which also improved with immunotherapy,²⁴ mild confusion and seizures and VGKC antibodies 1637 pm,²⁵ panic attacks, psychogenic non-epileptic seizures, delusions, hallucinations and confusion with VGKC Abs 42000 pM which was completely improved with immunomodulatory treatment.²⁶

Encephalitis Lethargica with antineuronal antibodies

In 2004, Dale et al²⁷ reported 20 patients who had remarkable similarity to the historical descriptions of Encephalitis lethargica : sleep disorder (somnolence, sleep inversion or insomnia), lethargy, parkinsonism, dyskinesias and neuropsychiatric symptoms. CSF examination commonly showed elevated protein and oligoclonal bands (OCB) (75 and 69% respectively). Investigation found no evidence of viral encephalitis or other recognized causes of rapid-onset parkinsonism. MRI of the brain was normal in 60% but showed inflammatory changes localized to the deep grey matter in 40% of patients. Furthermore, western immunoblotting showed that 95% of EL patients had autoantibodies reactive against human basal ganglia antigens. These antibodies were also present in the CSF in four patients tested. By contrast, antibodies reactive against the basal ganglia were found in only 2–4% of child and adult controls ($n = 173$, $P < 0.0001$). Rather than showing polyspecific binding, these antibodies bound to common neural autoantigens of molecular weight 40, 45, 60 and 98 kDa. Regional tissue comparisons showed that the majority of these autoantigens were specific to or enriched in CNS tissue. Immuno-histochemistry with secondary staining localized antibody binding to neurons

rather than glial populations. The authors proposed that this syndrome may be secondary to autoimmunity against deep grey matter neurons.

In 2005, Ances et al,²⁸ reported seven patients, who had developed subacute limbic encephalitis initially considered of uncertain aetiology. In the CSF, six had increased protein concentration, and three of five examined had oligoclonal bands. Six patients had antibodies to the neuropil of hippocampus or cerebellum, and one to intraneuronal antigens. Only one of the neuropil antibodies corresponded to voltage-gated potassium channel (VGKC) antibodies; the other five (two with identical specificity) reacted with antigens concentrated in areas of high dendritic density or synaptic-enriched regions of the hippocampus or cerebellum. Preliminary characteri-zation of these antigens indicated that they were diverse and expressed on the neuronal cell membrane and dendrites; they did not co-localize with VGKCs, but partially co-localized with spinophilin. All patients except the one with antibodies to intracellular antigens had dramatic clinical and neuroimaging responses to immunotherapy or tumour resection; two patients had neurological relapse and improved with immunotherapy.

In 2007, Bataller et al²⁹ reported a series of 39 patients, 19 of whom (49%) had antibodies to known antigens, and 17 (44%) to novel cell-membrane antigens (nCMAg). When compared with patients with antibodies to intraneuronal antigens, a significant association with response to immunomodulatory treatment was found in those with antibodies to cell-membrane antigens in general or to nCMAg.

In 2010, Irani et al³⁰ documented the clinical phenotype and tumour associations in 96 potassium channel antibody positive patients (titres >400 pM). Five had thymomas and one had an endometrial adenocarcinoma. Only three of the patients had antibodies directed against the potassium channel subunits. By contrast, antibodies were found against three proteins that are complexed with ¹²⁵I- α -dendrotoxin-labelled potassium channels in brain extracts: (i) contactin-associated protein-2 that is localized at the juxtaparanodes in myelinated axons; (ii) leucine-rich, glioma inactivated 1 protein that is most strongly expressed in the hippocampus; and (iii) Tag-1/contactin-2 that associates with contactin-associated protein-2. Antibodies to Kv1 subunits were found in three sera, to contactin-associated protein-2 in 19 sera, to leucine-rich, glioma inactivated 1 protein in 55 sera and to contactin-2 in five sera, four of which were also positive for the other antibodies. The remaining 18 sera were negative for potassium channel subunits and associated proteins by the methods employed. Of the 19 patients with contactin-associated protein-antibody-2, 10 had neuromyotonia or

Morvan's syndrome, compared with only 3 of the 55 leucine-rich, glioma inactivated 1 protein-antibody positive patients ($P < 0.0001$), who predominantly had limbic encephalitis. The responses to immunomodulatory therapies, defined by changes in modified Rankin scores, were good except in the patients with tumours, who all had contactin-associated-2 protein antibodies. Authors of this study concluded that the majority of patients with high potassium channel antibodies had limbic encephalitis without tumours.

Different authors published reviews^{31,32} about this latest form of encephalopathy to increase awareness of the physicians about this new entity.

Encephalitis with no known etiology

The threat of emerging infections and recognition of novel immune-mediated forms of encephalitis had raised the profile of this condition in recent years. Granerod et al³³ published a review of all published literature on incidence and etiology of encephalitis in non-outbreak settings and explored possible explanations for the large number of cases of unknown etiology. Annual incidence ranged from 0.07 to 12.6 cases per 100,000 population with an evident decrease over time ($p = 0.01$). The proportion of cases with unknown etiology was high across studies (>50% in 26 of 41 studies), with strong evidence of heterogeneity in study findings ($p < 0.001$). They concluded that new and emerging infectious agents, or new forms of immune-mediated encephalitis, may be responsible for cases currently of unknown cause and encouraged the ongoing global effort to identify these unknown causes.

Kennedy³⁴ in his review of viral encephalitis also remarked that in approximately half of cases the cause of encephalitis is not found. In another study from Finland, the etiology of encephalitis remained undefined in as many as 64% of patients, despite extensive laboratory evaluation.³⁵ The results of a recent surveillance study in the United Kingdom published in 2010 found that only 42% of patients with encephalitis had an identifiable infectious cause.³⁶

The California Encephalitis Project was initiated in 1998 to identify the causes and further describe the clinical and epidemiologic characteristics of encephalitis. From 1998 through 2005, a total of 1570 patients were enrolled. A confirmed or probable etiologic agent was identified for 16% of cases of encephalitis: 69% of these agents were viral; 20%, bacterial; 7%, prion; 3%, parasitic; and 1%, fungal. An additional 13% of cases had a possible etiology identified. Many of the agents classified as possible causes are suspected but have not yet been definitively demonstrated to cause encephalitis; these agents include *M. pneumoniae*

($n = 96$), influenza virus ($n = 22$), adenovirus ($n = 14$), *Chlamydia* species ($n = 10$), and human metapneumovirus ($n = 4$). A noninfectious etiology was identified for 8% of cases, and no etiology was found for 63% of cases.³⁷

In 2011, Ambrose et al on behalf of the UK Aetiology of Encephalitis Study Group,³⁸ reported on the etiology of encephalitis in 203 patients. An etiological diagnosis was made for 116 patients. Seventy-five cases (38%) were of unknown etiology. Sixteen (8%) of 203 samples were found to be associated with either *N*-methyl-D-aspartate receptor or voltage-gated potassium channel complex antibodies.

NMDA receptors

NMDA receptors are ligand-gated cation channels with crucial roles in synaptic transmission and plasticity. The receptors are heteromers of NR1 subunits that bind glycine and NR2 (A, B, C, or D) subunits that bind glutamate.³⁹ NR1 and NR2 combine to form receptor subtypes with distinct pharmacological properties, localization, and ability to interact with intracellular messengers. NMDA receptors are expressed on neurons throughout the brain; their highest densities are found in the amygdala, hypothalamus, prefrontal cortex, and hippocampus.⁴⁰ *N*-methyl-d-aspartate receptor antibodies are of the immunoglobulin G1 subclass and are able to activate complement on *N*-methyl d-aspartate receptor-expressing human embryonic kidney cells.

Over activity of NMDA receptors causing excitotoxicity is a proposed underlying mechanism for epilepsy, dementia, and stroke, whereas low activity produces symptoms of schizophrenia.^{41,42,43}

Encephalitis with anti-N-methyl-D-aspartate receptor (anti-NMDAR) antibodies

The California Encephalitis Project was specially designed to identify the etiologies of encephalitis. In the fall of 2007, a novel form of autoimmune encephalitis was described with the name anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. That same year, this form of encephalitis was observed in 1 case referred to the CEP, leading to a collaboration with the University of Pennsylvania to facilitate the recognition of this entity. In 2009, the first 10 cases of anti-NMDAR encephalitis identified at CEP were reported and compared with encephalitis cases resulting from viral etiologies.⁴⁴ Ten anti-NMDAR+ patients were profiled with a median age of 18.5 years (range 11-31 years). They had a characteristic progression with prominent psychiatric symptoms, autonomic instability, significant neurologic abnormalities, and seizures. In 2007, Sansing and colleagues⁴⁵ and then Iizuka et al⁴⁶ first described the characteristic syndrome that develops in several stages of illness and recovery in NMDAR antibody positive patients.

Since then NMDAR antibody positive encephalitis have been reported in all age groups of patients. Luca et al,⁴⁷ in 2011 reported three children with anti-NMDAR encephalitis. Immunosuppressive therapy resulted in near or complete recovery; however, 2 of the patients had early relapse necessitating re-treatment. Gabilondo et al,⁴⁸ also in 2011 studied relapses in anti-NMDAR encephalitis. A total of 13 relapses were identified in 6 patients. Four of them had several, 2 to 4, relapses. There was a median delay of 2 years (range 0.5 to 13 years) for the first relapse. Median relapse rate was 0.52 relapses/patient-year. Relapse risk was higher in patients who did not receive immunotherapy in the first episode ($p = 0.009$). Most cases (53%) presented partial syndromes of the typical anti-NMDAR encephalitis. Main symptoms of relapses were speech dysfunction (61%), psychiatric (54%), consciousness-attention disturbance (38%), and seizures (31%). Three relapses (23%) presented with isolated atypical symptoms suggestive of brainstem-cerebellar involvement. Relapses did not add residual deficit to that caused by the first episode.

Spillane et al⁴⁹ also reported about a 22 year old lady who had two episodes of self limiting encephalopathy 13 years apart and this patient's serum tested positive for antibodies to the NMDA receptor.

In 2010 Irani et al,⁵⁰ in their study of 44 NMDAR antibody positive patients of encephalitis observed relapses in 10 of 35 non-paraneoplastic patients (two to four relapses; time between relapses 3 months and 6 years) following some improvement after a previous episode. Overall, during their first episodes, five relapsers received no immunotherapy, three were only administered 3–5 days of intravenous glucocorticosteroids and two relapses occurred immediately after glucocorticosteroid withdrawal.

Davies et al,⁵¹ in 2010 identified N-methyl-D-aspartate receptor antibodies in six patients (two male and four female), who presented with a psychiatric prodrome, before developing seizures and obtundation requiring intensive care unit admission. After receiving immunotherapy three patients made a good but slow recovery; two were left with severe neurologic deficits; and one died.

Smith et al,⁵² in 2011 reported a 27-year-old woman who developed subacute progressive myoclonus, opsoclonus, and encephalopathy. Autoimmune cerebrospinal fluid screening revealed a neural-specific IgG that was confirmed to be N-methyl-D-aspartate receptor specific. The encephalopathy improved dramatically after plasmapheresis.

Nazif et al,⁵³ in 2012 studied 10 consecutive patients with Anti-N-methyl-d-aspartate receptor encephalitis (NMDARE)

to find out the prevalence, nature, and outcomes of cardiac dysrhythmias in patients with NMDARE. Patients were all female with an average age of 23 ± 5.5 years. Echocardiograms revealed structurally normal hearts with the exception of mild left ventricular hypertrophy in two cases. Eight patients had inappropriate sinus tachycardia. Six patients developed significant sinus bradycardia, which included periods of sinus arrest in four cases. Five patients manifested both sinus bradycardia and tachycardia. Bradycardia was often triggered by identifiable vagal stimuli. Temporary pacing was instituted in three patients, but permanent pacing was not required in any of the patients. In all cases, the dysrhythmias resolved with treatment of the underlying immune disorder with immunotherapy and/or teratoma resection. There was no evidence of dysrhythmia recurrence in any patient at follow-up. So the authors concluded that NMDARE had a predilection to cause severe sinus node abnormalities. Temporary pacing is occasionally required, but permanent pacing appears to be unnecessary.

In 2012, Takanashi et al,⁵⁴ reported from Japan about 5 children between 10 to 15 years of age who presented with delirious behaviour after infection with the 2009 H1N1 influenza virus. In all 5 patients, autoantibodies against N-methyl-D-aspartate type glutamate receptor were elevated or positive in cerebrospinal fluid or serum. Methylprednisolone (30 mg/kg per day for 3 days) or dexamethasone (0.4 mg/kg per day for 5 days) was administered to 3 patients. The outcome was excellent with no neurologic sequel in 4 of the 5 patients, and the autoantibody levels normalized in the 3 patients who had follow-up studies.

Finke et al,⁵⁵ in 2012 investigated cognitive performance in nine patients with proven anti-NMDAR encephalitis after recovery from the acute disease period (median 43 months after disease onset, range 23 to 69). Substantial persistent cognitive impairments were observed in eight out of nine patients that mainly consisted of deficits in executive functions and memory. Patients with early immunotherapy performed significantly better.

The field of autoimmune encephalopathies has expanded rapidly in the last few years. It is now well-established that a substantial proportion of encephalitides are associated with autoantibodies directed against the extracellular domains of cell-surface proteins which are critical in the regulation of neuronal excitability. These include LGI1, CASPR2, contactin-2 (VGKC-complex antibodies), and the NMDA, AMPA, and GABA(B) receptors.⁵⁶ Auto-antibodies with specificity towards intracellular proteins act as diagnostic markers of diseases that are usually associated with an underlying

cancer and are rarely immunotherapy-responsive. By contrast, antibodies that target the extracellular domain of surface-expressed neuronal proteins are likely to be pathogenic and their presence usually indicates the possibility of successful immunotherapy.⁵⁰

Synthesis of N-methyl-D-aspartate receptor antibodies

Irani et al⁵⁰ reported about 44 N-methyl-D-aspartate receptor antibody-positive patients from UK and Europe in 2010. They established a sensitive cell-based assay for detection of N-methyl-d-aspartate receptor antibodies in serum or cerebrospinal fluid, and a quantitative fluorescent immunoprecipitation assay for serial studies. Although there was marked intrathecal synthesis of N-methyl-D-aspartate receptor antibodies, the absolute levels of N-methyl-D-aspartate receptor antibodies were higher in serum than in cerebrospinal fluid. By serially diluting the 14 available paired samples to find detection endpoints, NMDAR-antibody titres were found to be between 6 and 450 times higher (mean 13.5) in serum than CSF. Except in one patient, there was clear evidence of intrathecal synthesis of NMDAR antibodies. The absolute concentrations of these antibodies had been found higher in serum than in the CSF in other studies also.^{57,58}

But Dalmau et al,⁵⁹ in 2008 first measured the integrity of the blood–brain barrier to determine whether patients had intrathecal synthesis of antibodies. Of 58 patients with paired serum and CSF available, 53 had preserved integrity of the blood–brain barrier. Analysis of normalized concentrations of IgG showed that all 53 patients had higher concentrations of antibodies in CSF than in sera, indicating intrathecal synthesis of antibodies.

Dalmau et al,⁶⁰ in 2011 also studied 413 patients (412 with paired serum and CSF) and encountered none in whom antibodies were only present in serum, suggesting intrathecal synthesis of antibodies. Antibodies were detected only in CSF, if diagnosis was delayed or patients had received treatment with plasma exchange or IV immunoglobulin.^{57,61,68}

Findings of other studies, in which NMDAR antibody concentrations were compared in serum and CSF, also suggested intrathecal synthesis of antibodies. Neuropathological analysis of the brains of five patients with anti-NMDAR encephalitis disclosed many infiltrates of plasma cells and plasmablasts in perivascular, interstitial, and Virchow–Robin spaces. The presence of these antibody-secreting cells supported the intrathecal synthesis of NMDAR antibodies.⁶² It is essential to determine whether there is intrathecal synthesis of antibodies. If antibody synthesis is taking place intrathecally, therapeutic

approaches that are effective in peripheral autoimmune disease—such as plasma exchange in myasthenia gravis—might not work.

Guidelines for testing for CNS Autoantibody:

With the detection of a varied group of antineuronal surface antibodies in patients presenting with encephalitis like syndromes, guidelines have been proposed for investigating such patients. In 2012, Lee et al⁶³ published “Autoantibody testing in Encephalopathies”, Zuliani et al⁶⁴ published “Central nervous system neuronal surface antibody associated syndromes: review and guidelines for recognition,” and Karim and Jacob⁶⁵ published “Immunological markers in neurological disorders.” In patients with features of Encephalitis they proposed that patients should ideally be tested for serum (paired with CSF if possible) antibodies to voltage-gated potassium channel (VGKC) complex antigens (leucine rich glioma inactivated protein 1 (LGI1), contactin-associated protein-2 (CASPR2) and contactin-2), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA), γ -aminobutyric acid-B receptors (GABA_BRs), glutamic acid decarboxylase (GAD), *N*-methyl-D-aspartate receptor (NMDAR) and for onconeural antibodies (particularly anti-Hu, anti-Ma 1/2, CV-2, and amphiphysin).

There is now unequivocal evidence that specific autoantibodies directed against neuronal proteins crucial to the control of neurotransmission are responsible for a proportion of cases of encephalitis in which no cause can be identified. Antibodies against two targets, the voltage gated potassium channel (VGKC) complex and the *N*-methyl-D-aspartic acid (NMDA) receptor, have emerged as two distinct entities. About 400 patients with clinically relevant raised VGKC complex or NMDA antibody titres have been identified at the UK diagnostic centre in Oxford in the past three years⁶⁶ and 400 patients with NMDA antibody associated encephalitis have been identified in the United States over a similar time period.⁶⁰

Features of Limbic Encephalitis associated with VGKC complex antibodies:

Limbic encephalitis associated with VGKC complex antibodies usually presents in middle aged or elderly people and is twice as common in men as in women.^{23,30,67} Vincent et al,²³ reported 10 patients (nine males and one female) whose median age was 57 years (range 44±79 years). Eight presented with combinations of impaired episodic memory, confusion and disorientation, and all patients developed these symptoms early during their illness. Seizures were present in nine patients during the acute phase of the disease,

including grand mal and/or complex partial seizures. Additional features included hallucinations, agitation and behavioural disturbance. Headache, drowsiness and loss of consciousness were not present in the patients. Parthasarathi et al²⁶ in 2006 reported that in the 25 cases of VGKC antibody-associated encephalopathy described till then, the main symptoms had been memory loss and seizures (usually of temporal lobe type).

Patients with VGKC complex antibodies typically develop personality change, amnesia (often with dense anterograde and retrograde components), and confusion over days to weeks, but they may also first present to psychiatric services with symptoms of agitation, hallucinations or behaviour change. Seizures are common and may contribute to confusion. A highly characteristic focal seizure disorder with very brief, frequent, unilateral dystonic face and limb jerking is often seen, and can predate the development of cognitive impairment.⁶⁸ About 60% of cases have low serum sodium consistent with the syndrome of inappropriate antidiuretic hormone (SIADH).^{23,30,67} A similar proportion have medial temporal lobe high signal on magnetic resonance imaging, consistent with localised inflammation, which if untreated may lead to focal hippocampal atrophy,²³ a substrate for both memory impairment and adult onset medial temporal lobe epilepsy.⁶⁹

Features of Encephalitis associated with NMDA receptor antibodies

Encephalitis associated with NMDA receptor antibodies is mainly seen in children and young adults, with women being affected about three to four times more often than men.^{50,59,60} About 70% of patients have prodromal symptoms consisting of headache, fever, nausea, vomiting, diarrhoea, or upper respiratory-tract symptoms. Between 1 and 21 days (median 7) before the onset of neurological disease, 11/44 (25%) patients, developed an infectious episode. Commonly the prodrome consisted of an upper-respiratory tract infection (n=6; one mycoplasma IgM, two anti-streptolysin-O antibodies), diarrhoeal illness (n=2; one with *Campylobacter jejuni* IgM), one meningitic presentation, and one infected mole. One 13-year-old female received diphtheria/tetanus/pertussis vaccination one day prior to seizure onset.⁵⁶ Within a few days, usually less than 2 weeks, patients typically present with psychotic features like hallucinations, delusions, hyper-religiosity, mania, paranoia, social withdrawal and thought disorder, or anxiety, or depression, which may initially be considered non-organic. In young children, the behavioural change can be difficult to detect because they often present with temper tantrums, hyperactivity, or irritability as opposed to frank psychosis.

In children, the first symptom to be recognized is often non-psychiatric—eg, seizures, status epilepticus, dystonia, verbal reduction, or mutism.⁶¹ There was then an inevitable progression, usually within a month, onto the second stage of more overt neurological features with movement disorder, characteristically of orofacial and choreoathetoid dyskinesias and stereotypical dystonic movements, epilepsy, autonomic disturbance and impaired consciousness, which often necessitates admission to intensive care.^{56,59,70} The most frequent autonomic manifestations include hyperthermia, tachycardia, hypersalivation, hypertension, bradycardia, hypotension, urinary incontinence, and erectile dysfunction.⁶⁷ More subtle phenotypes associated with lower NMDA receptor antibody titres include first episode psychosis⁶⁰ and adult onset focal epilepsy.⁵⁰ The full spectrum of symptoms associated with antibodies to both the VGKC complex and NMDA receptor remains to be determined.

Investigations:

Brain MRI is unremarkable in 50%⁷¹ to 89%⁵⁰ of patients. Abnormalities when detected include hyperintensities in T2 or FLAIR images in the hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem, and, infrequently, the spinal cord.

Electroencephalograms (EEG) are abnormal in most patients, usually showing non-specific, slow, and disorganized activity sometimes with electrographic seizures.⁵⁹ Slow, continuous, rhythmic activity in the delta-theta range predominates in the catatonic-like stage.⁶¹ This activity is not associated with abnormal movements and does not respond to antiepileptic drugs. In the study by Irani et al

EEG demonstrated epileptiform discharges in 50% of patients, usually early during the course of the disease, whereas generalized slowing in the slow theta or delta range was found in 80% patients, generally later during the disorder.⁵⁰

The cerebrospinal fluid (CSF) is initially abnormal in 80% of patients and becomes abnormal later in the disease in most other patients.⁵⁹ Findings include moderate lymphocytic pleocytosis, normal or mildly increased protein concentration, and, in 60% of patients, CSF-specific oligoclonal bands.⁵⁹ In the study by Irani et al⁵⁰ CSF analysis revealed lymphocytosis in only 68% of patients.

Brain biopsy does not provide a diagnosis of anti-NMDAR encephalitis. Biopsies in 15 patients showed normal or non-specific findings, including perivascular lymphocytic cuffing (predominantly of B cells), sparse parenchymal T-cell infiltrates, or microglial activation.^{59,72} Data from autopsy studies show similar findings along with plasma cells and rare or absent neuronophagic nodules.^{60,73}

Treatment:

There is no evidence based data to define treatment regimen in this newly established disease, but immunomodulatory treatment has shown marked improvement in a large proportion of these patients. In fact it is the uniform good response to treatment with immunoglobulin, plasma exchange and steroids which is the common factor amongst all these patients of autoimmune encephalitis. Treatment guidelines have been proposed by different groups which have experience in treating such patients. Irani et al⁵⁰ used different drugs in thirty-five of the patients who were treated

Table-I

Typical clinical features in 44 NMDAR-antibody positive patients⁵⁰

Early features

Higher cognitive dysfunction 40/44 (91%): confusion 29, behavioural changes 20, amnesia 14, dysphasia 13
Psychiatric 34/44 (77%): hallucinations 22, psychotic 20, agitation 18, depressive 12, anxiety 10, obsessive 1
Seizures 36/44 (82%): generalized 33, complex partial 16, simple partial 12

Later features

Spontaneous reduction in conscious level 20/44 (45%)
Movement disorder 39/44 (89%): choreoathetoid 30 (orofacial 27, upper limbs 22, lower limbs 10), parkinsonian 13, rigidity 10, myoclonus 7, oculogyric crises 3, opisthotonus 3, startle 2
Dysautonomia 32/44 (72%): tachy/brady-cardia 22, hyperhidrosis 12, persistent pyrexia 10, central hypoventilation 7, labile/high blood pressure 6, hypersalivation 4, pseudoobstruction 3, cardiac asystole 2

Total numbers of patients/total number (%). Anxiety was found as an isolated feature, without psychosis or depression, in only two cases. Data were provided by the referring neurologists. Although shown as early and later, there were some individuals in whom this distinction was not evident.

with immunotherapy: glucocorticosteroids (33 patients), intravenous immunoglobulins (15 patients), plasma exchange (13), cyclophosphamide (4), rituximab (2), azathioprine (1) and mycophenolate mofetil (1), or a combination of the above (23 patients).

Dalmau et al⁶⁰ has the experience of treatment of more than 400 patients suffering from this disease. They used concurrent IVIg (0.4 g/kg per day for 5 days) and methylprednisolone (1 g/day for 5 days) in preference to plasma exchange. Plasma exchange is more difficult to do in children, poorly cooperative patients, or patients with autonomic instability. If no response was seen after 10 days, second-line therapy was started. In adults, rituximab (375 mg/ml every week for 4 weeks) combined with

cyclophosphamide (750 mg/ml given with the first dose of rituximab), followed by monthly cycles of cyclophosphamide was used as second line therapy. This treatment was discontinued when patients have had substantial clinical recovery, which was usually accompanied by a decrease of CSF and serum antibody concentrations. Paediatricians often use only one of these drugs—mostly rituximab. After substantial improvement, antiepileptics are not needed in most patients. Because relapses occur in 20–25% of patients, continued immunosuppression (mycophenolate mofetil or azathioprine) was recommended for at least one year after initial immunotherapies are discontinued. These authors also proposed an algorithm for the treatment of anti-NMDAR encephalitis provided in Fig 1.

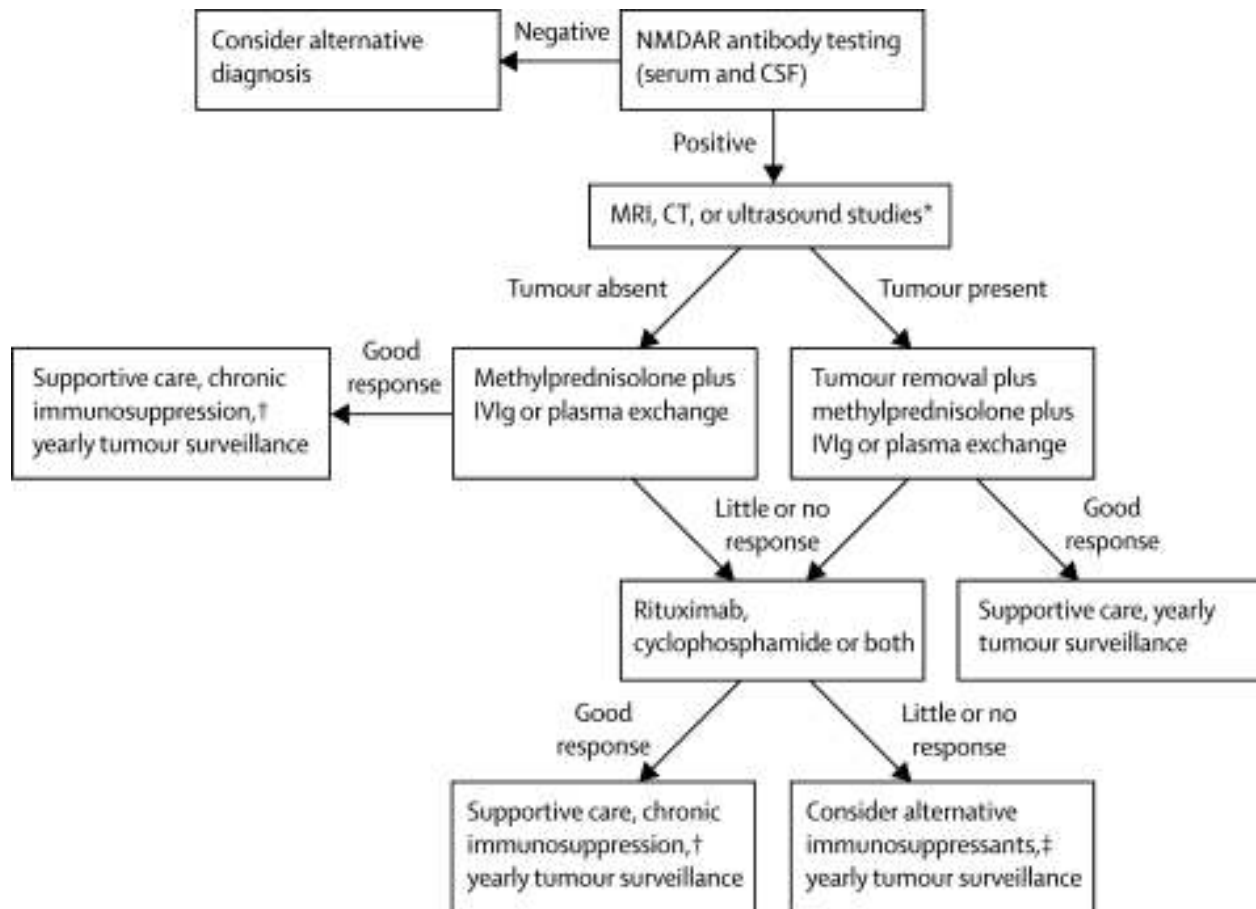


Fig-1: Proposed algorithm for the treatment of anti-NMDAR encephalitis ⁶⁰

*In women, ultrasound of abdomen and pelvis, or transvaginal ultrasound (if age-appropriate); in men, testicular ultrasound.

†Mycophenolate mofetil or azathioprine for 1 year. ‡Consider oral or intravenous methotrexate as an alternative immunosuppressant.

Mortality:

On the basis of data for 360 patients with clinical follow-up longer than 6 months, the estimated mortality for anti-NMDAR encephalitis was 4% (15 patients died).⁶⁰ 2 out of the 44 (4.54%) patients died in the series reported by Irani et al.⁵⁰ But Dalmau et al⁵⁹ reported from their previous study that about 75% of patients with NMDAR antibodies recover or have mild sequelae; all other patients remain severely disabled or die.

Recommendation:

Antineuronal antibody associated encephalitis is now an established entity. But awareness of this condition has to be increased amongst the doctors so that this potentially treatable condition is not missed. It is recommend that all individuals with a first presentation of psychosis, or people with psychosis and features of autonomic disturbance, movement disorder, disorientation, seizures, hyponatraemia or rapid deterioration should be assessed with the possibility of antibody-mediated encephalitis in mind. This assessment should include, as a minimum, a neurological and cognitive examination and early serum testing for antibodies against the NMDA receptor and voltage-gated potassium channel. Cerebrospinal fluid is not usually required. While awaiting antibody results, an electroencephalogram can be useful, as it may show encephalopathic features. Magnetic resonance imaging of the brain may well be normal (although the finding of temporal lobe signal change on imaging is very suggestive of an antibody-mediated encephalopathy), but is usually done to exclude any other pathology.⁷⁴ In developing countries like ours where extensive investigation is not possible, especially in rural areas, definite guidelines should be formulated so that physicians can treat these patients without excessive dependence on investigation. Since steroid treatment is easily available, not so costly and without major side effects in most cases, even therapeutic trials may be advocated with steroids in a presumptive diagnosis of autoimmune encephalitis.

Conflict of Interest : None

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