N-methyl D-aspartate receptor encephalitis: A new addition to the spectrum of autoimmune encephalitis

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Abstract

A large proportion of "encephalitis" is caused by unknown agents. Of late, a new category of disorders, "autoimmune encephalitis," has been described, which present with features similar to viral encephalitides. A well-delineated and common entity among this group is the recently described anti-NMDAR encephalitis (NMDARE). Although this entity was initially described in young women harboring ovarian teratomas, it is now characterised as well in children and men. Approximately 60% of the patients have an underlying tumor, usually an ovarian teratoma. In 40% of the patients, no cause can be found (idiopathic NMDARE). NMDARE typically presents with psychiatric features followed by altered level of consciousness, severe dysautonomia, hyperkinetic movement disorders, seizures and central hypoventilation. Orofacial dyskinesias resulting in lip and tongue mutilation are quite common. Seizures, are common and may be difficult to treat. The disease can be confirmed by serum and cerebrospinal fluid anti-NMDAR antibodies. Titers of these antibodies can also guide response to treatment. Tumor removal is necessary if identified, followed by immunological treatment. Intravenous methylprednisolone and immunoglobulins aim to suppress/modulate immune response while plasma exchange attempts to remove antibodies and other inflammatory cytokines. Rituximab and cyclophosphamide aim to suppress antibody production. Recovery is slow and often with neurological deficits if treatment is delayed. With many distinctive clinical features, a specific antibody that aids diagnosis, and early effective treatment with commonly available drugs leading to good outcomes, NMDARE is a diagnosis that should be considered early in any case of "unexplained encephalitis."

Key Words

Autoimmune encephalopathy, autoimmune encephalitis, limbic encephalitis, N-methyl D-aspartate receptor encephalitis, paraneoplastic encephalitis

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Introduction

Neurologists are often confronted with an encephalitic illness. They affect any age group with a wide spectrum of clinical presentation, the most common being headache, lethargy, fever, behavioral and personality changes leading on to drowsiness and seizures.[1] The annual incidence of encephalitis in the community is estimated to range from 3.5 to 7.4 cases per 100,000 population.[2] Most are presumed to be infectious in origin and, in fact, more than 100 pathogens have been identified as a causative agent. However, often, no clear pathogen is identified.

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Autoimmune encephalitis (AIE) is an exciting new group of disorders that is eminently treatable and should be considered in the routine differential diagnosis by every neurologist early on in the course of the illness. In this review, we provide the differential diagnosis of AIE and then focus on anti-NMDA (N-methyl D-aspartate) receptor antibody encephalitis (NMDARE). The first Indian case was recently described by one of us (BVM).

Epidemiology

A recent study has provided insights into the likely burden of "encephalitic illness." Of 203 patients with an encephalitic illness, 42% had an infectious cause (including 19% with Herpes simplex encephalitis, 5% with Varicella encephalitis and 5% with *Mycobacterium tuberculosis*), 37% were of unknown cause and 21% had immune-mediated encephalitis (IME). Of the last category, 11% were diagnosed as acute disseminated encephalomyelitis (ADEM), while 9% had other autoimmune causes. Among this subgroup, 1% of the patients were diagnosed with anti-NMDAR encephalitis,[3] a figure similar to that observed by Dalmau *et al.*, who also found only six cases in a large series of 505 patients (1%).[4]

Definitions and nosology

It is easier to understand this category of illnesses in terms of neuroanatomical involvement. The common clinical presentations of AIE can be subdivided into limbic, diencephalic, brainstem encephalitis and encephalomyelitis. Patients with limbic encephalitis usually present with short-term memory loss, seizures, confusion, hallucinations, mood disorder and personality change. The psychiatric manifestations can be prominent at the onset, the neurological features appearing later. The triad of anterograde amnesia, seizures and psychosis is fairly classic of limbic encephalitis.

Diencephalic encephalitis presents with features of hypothalamic–pituitary dysfunction. Patients develop excessive daytime sleepiness (EDS), narcolepsy–cataplexy (with low cerebrospinal fluid hypocretin), hyperthermia, change in weight (usually weight gain) or sexual dysfunction.

In brainstem encephalitis (rhombencephalitis) cranial neuropathy, ophthalmoparesis, parkinsonism, dysarthria or dysphagia lead on to a lowered level of consciousness.

In the encephalomyelitic variant, features of myelopathy and/or spasms and rigidity are also noted. However, it is essential to note that patients may present with a forme fruste of a particular syndrome, and the full-blown picture can take time to develop. Table 1 lists some of the common AIEs.

Anti-NMDA Receptor Encephalitis

Background

The original descriptions of anti-NMDA (N-methyl D-aspartate) receptor encephalitis (NMDARE) were confined to young women with ovarian teratomas, and was named acute juvenile non-herpetic encephalitis or ovarian teratoma-associated limbic encephalitis (OTLE) in Japan. Subsequently, Dalmau *et al.* published a seminal paper describing a series of 100 patients and detected the disorder in men and children also.[5] The disorder was correlated with the presence of an antibody directed against the extracellular N-terminal domain of the NR1 subunit. The antibodies reduced the numbers of cell-surface NMDA receptors and receptor clusters in postsynaptic dendrites, an effect that was reversible when the antibody levels decreased. Anti-NMDAR antibody (NMDARAb) was found in both serum and CSF samples of patients. Often, CSF NMDARAb titers in the CSF were higher than in the serum and CSF antibody levels correlated better with the stage of the disease.

Table 1: Common autoimmune causes of encephalitis

- Paraneoplastic limbic encephalitis (antibodies to Hu, Ri, Ma1 and Ma2, Cv2, amphyphysin and Tr)
- Steroid responsive encephalopathy
- With thyroid antibodies (Hashimoto's)
- Without antibodies
- Inflammatory vasculopathies; CNS vasculitis, SLE, APLA, Susac's, Sjogren's
- Thymoma-associated paraneoplastic encephalitis* (TAPE)
- Voltage-gated potassium channel (VGKC) encephalopathy*/ Morvan's syndrome
- Anti-NMDAR encephalitis (NMDARE)*
- AMPA receptor antibody-associated encephalitis
- $GABA_B$ receptor antibody-associated encephalitis
- Glycine receptor antibody-associated encephalitis

Putative disease mechanisms

The NMDA receptor (NMDAR) is a ligand-gated cation channel involved in synaptic transmission. NMDAR is composed of two heteromers, NR1 and NR2. NR1 primarily binds glycine, whereas NR2 binds glutamate. The combination of these heteromers leads to a receptor with complex functions, the overactivity of which leads to epilepsy, strokes and dementia, and the underactivity putatively causes schizophrenia.[6,7] Moreover, the use of NMDA antagonists such as Ketamine or PCP [phencyclidine/ "angel dust"] in individuals produces the same clinical picture, strengthening the hypothesis.

As NMDA receptors are widely distributed across the brain, their blockade produces myriad effects. Anti-NMDA receptor antibodies predominantly block the GABAergic neurons, leading to a disinhibition of the excitatory pathways and increased extracellular glutamate. The resulting fronto-striatal syndrome is characterized by psychosis, catatonia, mutism and dystonia. The brainstem central pattern generator, which is normally inhibited by the GABAergic systems, is disinhibited, leading to the orofacial dyskinesias and the involuntary movements of the limbs and trunk. The ubiquitous presence of NMDAR in the dopaminergic, cholinergic and noradrenergic systems and the resultant hypofunction may explain the dysautonomia. Finally, a direct effect of the antibodies on the nucleus of Kolliker-Fuse or the ponto-medullary respiratory network could explain the respiratory dysfunction.

Anti-NMDA Ab binding to NMDAR leads to internalization of the receptors by the cell, decreasing the synaptic density and synaptic localization of NMDA clusters.[8] The NR1 antibodies affect the NMDA receptors selectively (without affecting the nearby receptors) and abolish NMDA-mediated synaptic currents. The magnitude of the changes is directly proportional to the antibody titer, and is reversible as the titer reduces. Moreover, the higher CSF titers compared with serum can be explained by intrathecal synthesis.

Ovarian teratomas express NR1; immune cross-reactivity likely leads to abnormal host–immune response that is largely confined to the central nervous system.[5]

In about 50% of the patients Mycoplasma pneumonia serum IgM is positive. Although the significance of this is unknown, infections may trigger an autoimmune encephalitic process akin to PANDAS (pediatric autoimmune neuropsychiatric illness associated with streptococcal infections) mediated by antistreptococcal–antineuronal antibodies.[9]

Clinical features

Dalmau's series of 100 patients reported an age range of 5–76 years, with a mean age of 23 years[5]. Majority of the patients were women (91%). Subsequently, another series of NMDARE detailing the disorder in children and adolescents was published in which the youngest patient was 2 years old.[10] The disorder may evolve over five phases. In the initial "prodromal

phase," the patient suffers from a "flu-like" illness. In the second "psychiatric phase," behavioral disturbances, psychosis, hallucinations, anxiety, agitation and paranoia supervene; temper tantrums or hyperactivity dominate in children. Usually, most patients are evaluated by psychiatrists at this stage. By stage three, the neurological nature of the illness is evident. Patients develop alteration of sensorium (88%) and seizures (76%). Partial seizures with faciobrachial involvement are common. Frank dysautonomia (70% of patients), including cardiac arrhythmias, hypo or hyperthermia, central hypoventilation (66% of patients), unexplained pyrexia, apneic spells and blood pressure fluctuations complicate this phase, and admission into intensive care is necessary.

By phase four (hyperkinetic phase), movement disorders such as oro-facial dyskinesias, bruxism, lip and tongue biting, dystonia, complex stereotyped movements, ophisthotonus, oculogyric crises and choreic movements are observed in around 86% of the patients.[5] Severe teeth grinding, loss of teeth, mutilation of lips and tongue, flinging movements of extremities, joint subluxations, bruising, fractures, muscle ruptures, exhaustion and rhabdomyolysis can occur during this phase. Autonomic storms can accompany the hyperkinetic phases. Movements can also be intensified by sensory stimulation and subside when the patient is sedated.

Phases 4 and 5 are usually combined and, during these phases, patients are often unresponsive for long periods of time and lie with eyes open, mute or mumbling incoherently in a state resembling catatonia (wakeful unresponsiveness).[11] By phase five, recovery begins with gradual return of awareness and responsiveness. Some patients are left with cognitive deficits – memory dysfunction, frontal lobe signs, behavioral and attention deficit disorders . NMDARE is potentially fatal if unrecognized, but reversible if recognized and treated early. Even so, the course of the disease can be prolonged and patients can take months to years to recover.

Illustrative cases

A 22-year-old woman was brought to the psychiatry unit with bizarre hallucinations and personality changes of 1 week duration. She was started on antipsychotics and admitted to the unit. Three days later, she developed a strange gait with occasional buckling at the knee and stuttering speech. The dose of antipsychotics was increased; however, she became increasingly drowsy and developed seizure-like activity. Repeated EEGs were normal. However, by this time, complex stereotyped movements of her limbs had set in. VEEG started showing frequent right frontal onset seizures with secondary generalization. She was started on multiple anticonvulsants, intubated and mechanically ventilated. Even with eight anticonvulsants and midazolam/propofol infusions, the EEG continued to show nonconvulsive seizures. Two days later, severe dysautonomic features including fluctuating blood pressures and tachy–bradycardia were observed. CSF exam showed 25 cells with 80% lymphocytes, 20% neutrophils, normal protein and sugars. All routine cultures and polymerase chain reaction (PCR) tests were negative. A serum and CSF NMDAR antibody was sent and presumptive treatment for NMDARE was started with IVIG 2 gm/kg x 5 days. After 7 days, the EEG showed resolution of seizures and anticonvulsants were tapered. However, intractable oro-facio-lingual dyskinesias supervened and she started biting her tongue and lips. Haloperidol, Tetrabenazine, clonazepam, Diazepam and anticonvulsants were tried again but to no avail. The movements were seen to wax and wane. After 3 weeks, the NMDAR antibodies were reported as highly positive (Oxford, UK). The patient was gradually weaned off mechanical ventilation. She continued to have severe choreiform movements of the limbs, trunk and oro-facio-lingual dyskinesias, which waxed and waned, and were associated with autonomic storms. Some of these were precipitated by tactile, auditory or visual stimuli. She remained comatose during this period. She underwent an ultrasound abdomen, computerized tomography (CT) abdomen and chest, magnetic resonance imaging (MRI) abdomen and wedge biopsy of the ovaries to detect an occult ovarian teratoma. All of these were inconclusive. As the movements persisted after 3 months with autonomic storms, another course of IVIG was given and a repeat serum and CSF sample were assayed. As the titers remained high, she was administered Rituximab. At 5 months, she continued to have abnormal movements and her sensorium had not improved. Her family was unwilling for prophylactic oophorectomy or cyclophosphamide therapy. She was continued on monthly IVIG maintenance therapy. At 6 months, a third CSF NMDAR Ab assay showed low titers and IVIG was discontinued. Her sensorium started improving, abnormal movements gradually decreased and she was transferred to the ward. She was finally discharged home after 8 months. At follow-up 1 year later, she still has residual cognitive impairment, recent memory impairment, infrequent seizures, was taking three anticonvulsants and had not resumed her prior occupation yet. She will continue to remain under periodic surveillance for an ovarian teratoma.

Management

It is important to note that when patients present with an "acute encephalitic" illness, it is clinically difficult to distinguish infective from noninfective encephalitis. In fact, infectious causes are far more common than autoimmune ones, and should be ruled out.

CT scans of the brain are usually normal. MRI of the brain may also be normal or may demonstrate nonspecific abnormalities in the T2-weighted or FLAIR sequences in the mesial temporal lobes, cerebral cortex, cerebellum, basal ganglia or brainstem. Contrast enhancement is unusual and transient meningeal or cortical enhancement can be encountered. Serial MRIs can show cerebral atrophy.

Lumbar puncture is immensely helpful and usually demonstrates a lymphocytic pleocytosis with a mean count of 26 cells on presentation (five to 200 cells) in about 68–90% of the patients.[12] CSF protein levels are elevated and glucose levels are often normal. The CSF IgG index is elevated, indicating intrathecal antibody synthesis, and CSF oligoclonal bands are seen in about 50% of the patients. CSF anti-NMDAR antibodies are highly positive and titers correlate with the disease process.[13] CSF viral PCR and cultures should be negative. A few patients show a positive mycoplasma serology; however, the significance of this test in NMDARE is unclear.[10]

EEG may show electrographic seizures (10%) or, more frequently, shows generalized or fronto-temporal polymorphic

slowing. One of our patients had seizures lasting up to 3 weeks that required up to nine anticonvulsants before seizure control was achieved.[14] Often, complex stereotyped nonepileptic movements can be seen that are difficult to distinguish from seizures without EEG monitoring.

In stage III, seizures, dysautonomia and hypoventilation are a major management issue. Patients often need continuous EEG monitoring and intubation, tracheostomy with attendant complications.

Movement disorders can be resistant to medications and require sedation, including propofol or even neuro-muscular blockade at times, to prevent lip and tongue injury and loss of dentition. Benzodiazepine infusions (midazolam) or even high-dose diazepam (30 mg/day) through a nasogastric tube can be effective in controlling the dyskinesias.[15] Cardiac dysrhythmias can be life-threatening. Some patients will require a pacemaker to prevent severe symptomatic brady/tachyarrhythmias.

A diligent search for an ovarian teratoma is necessary. In approximately 60% of the women, an ovarian teratoma is found by abdominal ultrasound, CT scan or MRI of the pelvis. Often, the tumors are tiny (ranging from microscopic to 22 cm in size) and teratomas can be mature or immature. To detect the microscopic teratoma, an exploratory laparotomy is warranted in refractory cases when management fails and illness seems refractory. Younger patients (<18 years of age) are less likely to have tumors (27–31%) as compared with older patients (>18 years of age), where the frequency is 55–60%.[13]

Rarely, an extra-ovarian teratoma such as a mediastinal teratoma, Hodgkin's lymphoma, testicular tumor or small cell lung carcinoma is the underlying culprit. Tumor resection is the primary modality of treatment. It is often combined with immunotherapy such as IV methylprednisolone, IVIG, plasma exchange (PLEX), Rituximab or cyclophosphamide. In most instances, IVMP, IVIG or PLEX are used initially. Additional courses of these can be used if necessary. If there is no clinical improvement and CSF titers remain high at 1 month, then one can consider Rituximab or cyclophosphamide.[12]

It is sometimes difficult to clinically judge the treatment response and decide on escalating therapy. CSF/serum titers of NMDAR antibodies may be helpful in guiding therapy. Plasma exchange and IVIG can reduce the serum NMDA antibody titers quickly.[16] CSF titers on the other hand decrease more slowly and seem to correlate better with the clinical picture.

In about 40% of the patients, no underlying tumor can be demonstrated. Patients with a paraneoplastic NMDARE seem to have a better outcome than idiopathic NMDARE.

Prognosis

Nearly 75% of the patients make a good recovery following tumor removal and/or immune-modulatory treatments, although the time to full recovery is variable (1–14 months), with a median of 2.5 months. Importantly, serial NR1 NMDARAb levels seem to correlate with clinical severity over time in patients.[12] Hence, static or persistently elevated levels of antibodies in CSF may signify a recalcitrant type of NMDARE, which will require aggressive immunotherapy combined with tumor removal. Generally, recovery is more favorable in patients with an underlying tumor than in the idiopathic cases. Some patients, especially idiopathic NMDARE, may take up to 3 years for complete recovery. Nearly one-third of the patients experience a relapse (25%) within 18 months, although it may occur as late 7 years after the original illness.[5]

In some patients, a relapse can be associated with the reappearance of a second teratoma. At present, periodic surveillance with ultrasound or MRI of the pelvis is recommended yearly.

The complications of NMDARE can be divided into neurologic and general disorders. The neurological sequalae include hemi, quadri or tetraparesis, aphasia, signs of frontal lobe hypofunction (apathy, disinhibition, lack of planning and poor judgment) and sleep disturbance. General complications include joint contractures, bed sores, pulmonary embolism, nosocomial pneumonia, rhabdomyolysis, self-mutilation, loss of teeth, joint subluxations and fractures.

Although serial MRIs may show brain atrophy, this is at least partly reversible over years, indicating a functional component that may partly explain the better prognosis compared with viral encephalitides.[16]

Conclusions

The differential diagnosis of encephalitis should include the category of AIE from onset, until an adequate alternative etiology is identified. The disorders in these categories are potentially fatal if unrecognized or recognized too late, but are eminently treatable and reversible.

NMDARE is one of the AIE; the combination of psychiatric illness followed by lowered levels of consciousness, hyperkinetic movement disorders (especially oro-facial dyskinesias), dysautonomia and central hypoventilation should arouse the suspicion of NMDARE and initiate the search for an underlying ovarian teratoma. The similarity of this illness to "encephalitis lethargica" or Japanese B encephalitis [JE] is striking, and presumed JE cases with negative serology should be further investigated to rule out NMDARE.

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