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Horror Auto Toxicus and Brain-Our Experience with Review

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Abstract

The immune system is a dynamic, reactive surveillance system. Some genes influence immune responses, cell to cell communication which either facilitate or protect against neuroimmunological disorders. Dysregulation at this level seems to have a role in a large spectrum of neurological disorders opening up a new window to therapy. A good number of syndromes are definite entities, and others are probable in this group. Clinically subacute encephalopathy with diarrhea, ovarian teratoma, facio-brachial dystonic seizures, and the triad of panic, catatonia, and sleepiness are classical pointers. EEG is mostly non-specific except for the extreme delta brush of NMDA and helps differentiate the immediate differential diagnosis of SSPE, CJD, and HSV. Imaging has patterns recognizable in conditions like clippers or can be normal. Antibodies seem to be the definite tool, but there can be unknown antibodies. A high degree of suspicion is important for diagnosis.

Keywords: Autoimmune encephalopathies, the red herrings, new therapeutic avenues, Biomarkers

Key Message : *Autoimmune disorders are essential to recognize as therapeutic options are good if diagnosed early.*

Introduction

The word **horror of self-toxicity** was coined by German bacteriologist Paul Ehrlich (1854-1915). Generally, our immune system is protective of self. (1). He said that goats made an antibody to other goat cells but not self; this was made possible by silencing the self-receptors in self-reactive lymphocytes, a type of T-cells called dendritic cells produced in the thymus (2). Several antigen-presenting cells and DC cells play a role in capturing and eliminating these cells before they are presented to MHC 1 & 11 peptide complexes (3). Self-reactive T and B cells are deleted centrally, and non-self-reactive ones replace the B cell receptors. But, at times, they escape this deletion and editing process, as first postulated by Burnett in his Clonal Selection Theory(4). Also, foreign antigens can cross-react with self-antigens and modify their phenotype. During maturation, there is increased formation of stable MHC–peptide complexes, better expression of membrane molecules like CD86 and other B7 family members for T cell binding and activation, synthesis of cytokines that influence T cell proliferation and differentiation, production of chemokine receptors that enhance the movement of DCs into lymphatic vessels and lymphoid organs. Organisms induce pattern recognition receptors. There is a molecular communication network and pathogen recognition receptors. Genes influence immune responses, cell to cell communication and either facilitate or protect against disorders. Epigenetic influencing factors are Tobacco, lack of exposure to pathogens in early life, EB virus infection, environmental radiation, vaccines, etc.

This suggests that DCs in the steady state, before infection or inflammation, critically define immunologic self and prevent the induction of autoimmunity and chronic inflammation against environmental proteins. Per this theory, proteins captured and processed by DCs in a steady state are tolerogenic, i.e., the DCs silence the corresponding antigen-specific T cells. Because of this, during infection, the immune response focuses on the pathogen, not self-antigens. Autoimmune diseases occur when this mechanism becomes dysregulated, and self-antigens are targeted. When the brain becomes the target, it results in the syndrome of noninfective Encephalitis.

What are the unique immunological features of CNS?

The immune system is a dynamic system that replicates, regenerates, and adapts. A single lymphocyte circulates in surveillance twice in 24 hours. But surveillance is not regular in restricted

immune organs like the nervous system. The cerebrospinal fluid does not have neutrophils, unlike other body fluids, but the brain has parenchymal, vascular, meningeal, and CSF barriers. Neuronal cells are not very capable of replicating like other organs, even though plasticity exists. There is a blocking of entry of T cells to the CNS, which partly protects the nervous system from autoimmune diseases. Damage depends on the antigen type and site affected; a cytokine produced like TNF –α, immune cells, glial cells, and neurons act together to modulate pain, infection, and inflammation. Hypothalamus is the main transducer of information to the immune system, carried out by β-messenger molecules, and the immune system talks to the hypothalamus via immune transmitters. The ventromedial hypothalamus has a role in antibody formation. (5)

What is Encephalitis?

Encephalitis is acute or subacute brain inflammation and usually happens in not more than six weeks (6). It affects all age groups and causes significant disability. Though the common cause is infective, the noninfective need to be recognized when fever and CSF Pleocytosis are lacking and neuropsychiatric symptoms with or without seizures are present. A noninfective encephalitis is a group of eminently treatable conditions if diagnosed early; a high degree of suspicion is important in every possible case. When the Core symptoms of cognitive and psychiatric dysfunctions are seen, AD and Bv - FTD become other possibilities if the course is slow and protracted. A good number also are diagnosed with primary mental illness. Some patients even receive ECT. Many situations are so atypical that suspicion is complex. Antibody testing is not available to all patients. Therefore the response to therapy as criteria for diagnosis is not practical to apply in the long term, and false response to immunomodulation can be seen with conditions like lympho reticular neoplasms. At the bedside, immune-mediated Encephalitis is classified as possible and probable with no need for antibodies and definite with antibody positivity (7). Infective and other causes should be excluded in all cases. Delirium, working memory deficit (problems in temporary storage and manipulation of information, confusion, mood changes, short-term memory impairment, and seizures are common.

There are three categories of antibodies. The ones which target intracellular antigens in the nucleus or cytoplasm, which are often associated with cancer, and the other group targeting membrane antigens like protein receptors and ion channels, 3rd category targets the enzymes, e.g., GAD 65 targeting cytoplasmic enzymes. Even PD, AD, CVA, Seizures, and infections are found to have immune dysregulation, opening up novel therapeutic options.

Possible

When all the below points are there;

1. Progression in less than three months, neuropsychiatric features, short-term memory loss, altered mental status.
2. New focal CNS signs, seizures, MRI evidence of Encephalitis, CSF of more than five cells.
3. Exclusion of other causes.

Definite when all the four points are there:

1. Progression in less than three months, neuropsychiatric features, short-term memory loss, altered mental status.
2. MRI bilateral medial temporal FLAIR changes.
3. One of the following; CSF pleocytosis, more than five cells, EEG changes in temporal regions.
4. Exclusion of other causes

Many of these patients land with psychiatrists and red herrings lead to psychiatric diagnoses. This results in the loss of valuable time. EEG is a simple tool easily accessible, and all patients with new onset neuropsychiatric syndrome need to be screened with an EEG(8).

Triad for clinical suspicion

When we compared the clinical features between the Autoimmune encephalitis group (comprising of both NMDA and VGKC groups) and degenerative dementias, there were significant differences among both groups for Panic, Catatonia, sleep, and seizures. This simple bedside TRIAD of panic and sleepiness with either catatonia or attacks, if found in patients, is an indicator to order antibody assessment before anything else is planned (9). (Utility of a Novel Clinical Triad (Chandra's TRIAD) for Early Diagnosis of Autoimmune Encephalitis (AIE) in Patients with Progressive Cognitive Decline .journal of aging science. Commentary Thomas Gregor Issac* Department of Geriatrics Psychiatry Unit, National Institute of Mental Health and Neurosciences, Bengaluru, India.)

Epidemiology

The prevalence of autoimmune Encephalitis is almost equal to infections (10) 13.7/100,000 as of 2014. The incidence rates 0.8/100,000 and 1.0/100,000 person-years respectively 1995. The number of recurrences is more in autoimmune than infectious Encephalitis (p=0.03). It is higher among African-Americans. In India, the prevalence reported is not well known.

Definition of terms

What are immune-mediated dementias?

Molecular mimicry of neuronal proteins by tumor cells and infections causes cross-reaction and inflammation in the nervous system. Some of these antibodies cause specific syndromes. LE or limbic encephalitis is caused by anti-Hu, anti - CV2, anti-Ma 2, and anti-VGKC. The tumor associations are small cell lung tumor with anti-Hu, anti NMDAR with ovarian teratoma, and anti-Ma 2 with testicular cancer. Tumors can have multiple antibodies too. Other symptoms caused are Ataxia, opsoclonus myoclonus syndrome, diffuse multifocal encephalon myelitis, etc.

Limbic Encephalitis is characterized by amnesic syndrome, depression, emotional lability, personality change, Ataxia, seizures, and hypothalamic involvement like hypersomnolence. CSF shows a mild increase in proteins and cells. OCB can be seen in a small percentage. MRI can be normal to T2 FLAIR hyperintensity in mesial temporal and limbic regions with or without enhancement.

Clinical assessment and Tools

Evaluation of suspected patients consists of a CSF study that shows less than 100 white blood cells per mm in most patients. There is an elevated IgG index or oligoclonal bands in about 50%. But these features are in LGI1 and create suspicion of non-inflammatory encephalopathy. Paraneoplastic antibodies Hu and Ma2 are poorly responsive to treatment. Neuronal cell surface antibodies to LGII, GABA B receptor, AMPA receptor, and GAD present as limbic Encephalitis.

Evaluation is clinical, electrophysiological, and Biomarker, which includes radiology and antibodies. Complete blood count, electrolytes, glucose, calcium, thyroid function, vitamin B12, and folates are recommended to pick up other reversible forms, including infection, renal failure, hypo- or hypermagnesemia, hyperglycemia, hypo- or hypercalcemia, hypo- or hyperthyroidism, liver function, syphilis, Lyme disease-Borrelia, and HIV. Aβ 42 and tau protein in CSF is useful to detect potential AD but are not routinely recommended. CSF can show false positive elevated measles antibody titers, and therefore correlation with clinical and EEG features is important. When in doubt, antigen-based tests should be done to prevent labeling a reversible condition as a fatal disease SSPE. (11) CSF antibodies are important for the following reasons. Sometimes antibodies are seen in CSF and not a serum. CSF and serum can have different antibodies, e.g., NMDA in CSF and GABAa in serum, and disease is correlated to

CSF. CSF changes correlate with the disease better, and serum and cell-based assays have more false positives and negatives. (12).

Cell surface antigens or synaptic antigens

They act on the extracellular epitope of the antigen. These are mostly reversible. They are different from the paraneoplastic syndromes, which affect the intracellular proteins. Negative results do not exclude an autoimmune disorder.

1. Anti-NMDAR Encephalitis

An anti-neuronal antibody disease of childhood. This is a polysymptomatic disease with progressive neuropsychiatric symptoms and seizures, autonomic dysfunction, catatonia, aphasia, hyperkinetic movements, and hypoventilation. Children can have Ataxia, hemiplegia, speech deterioration, hypertension, tachycardia, hyperthermia, and central hypoventilation. Testing antibodies against NMDAR NR1/NR2 heteromers is diagnostic. CSF IgG antibodies against the GluN1 subunit of the NMDA receptor are the hallmark. There is a reduction in surface NMDAR, causing altered synaptic function. Ovarian teratomas are seen in 56% of older girls more than 18 years and 31% less than 18. This can follow HSV encephalitis and systemic viral infections (13). The antibody to apoptotic tumor cells are processed in regional lymph nodes, the memory B cells promote antibody production by plasma cells, cross BBB, and cross-reacting antibodies are synthesized. The antibody has an effect on plasticity, synapses, and behavior. CSF Pleocytosis and oligoclonal bands, Ovarianteratomas are seen in older patients, but in adults, more than 45 years, tumors are less, and when present, it is carcinoma. EEG shows infrequent epileptic activity but frequent slow, disorganized activity or extreme delta brush frontally maximal high-voltage beta activity superimposed on frontally maximal delta waves (figure1).

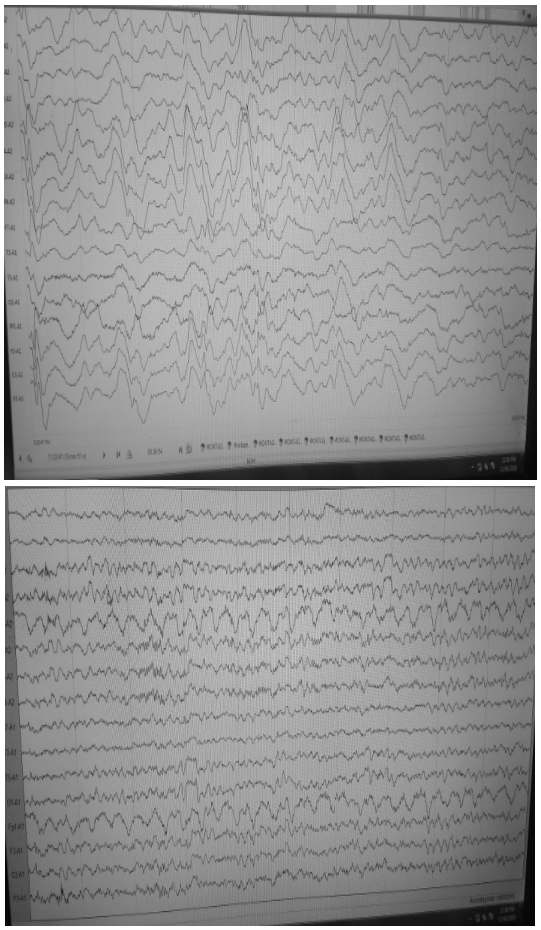

Figure 1*. Shows extreme delta brush showing frontal dominant delta with high voltage beta*

Clinically it is categorized as probable if Rapid onset in less than three months and 4 out of 6 among abnormal behavior, speech dysfunction, seizures, movement disorders, autonomic dysfunction, and altered consciousness. There are five phases described;1. Prodrome phase: Flu-like illness. 2. Psychiatric phase: Behavioral change, Psychosis, Hallucinations, Anxiety, agitation, paranoia, Temper tantrums, or hyperactivity 3. Neurological phase: Altered sensorium (88%), Seizures (76%), Dysautonomia (70%).4. Hyperkinetic phase: (86%) Orofacialdyskinesias, lip and tongue bite, Complex stereotyped movements, Ophisthinus, oculogyric crisis, choreic movements. 5. Recovery phase: Gradual return of awareness and unresponsiveness, Left with cognitive dysfunction, Potentially fatal if unrecognized. Exclusion of other causes is important. Sometimes overlaps with MOG-related

or aquaporin 4 (AQP4)-related syndrome. MRI in anti-NMDAR Encephalitis is variable. A good number have normal MRIs. FLAIR signal abnormalities can be found in the cortex, basal ganglia, meninges, and brainstem. Treatment options are high dose steroids1gram MP for five days with and IVIg0.4 gms/kg IVIg /day for five days. If a response is not seen in 15 days, Rituximab is given. It prevents plasma cell formation by eliminating B cell lineage. The dose is 375 mg/m2 weekly for four weeks and also monthly cycles of cyclophosphamide 750 mg/m2 for 4–6 months which interferes with DNA replication and eliminates T regulatory cells. PE is cheap but does not remove the intracranially synthesized antibody. (14)

2. V GKC-Encephalitis

Voltage-gated potassium channels (LGI1 and CASPR2), i.e., Leucine-rich, glioma inactivated one and Con- tactic associated Protein 2.

LGI1 LE presents with memory deterioration, FBDS, other kinds of seizures, psychiatric disorders, confusion, and hyponatremia. LGI1 receptors are targeted by antibodies, a secreted protein that interacts with pre and postsynaptic epilepsy-related receptors. Affects older men than women. Most cases of anti -VGKCE is not associated with tumors. It can be associated with neuromyotonia. The classical facial-brachial dystonic seizures are seen in adults, brief but refractory to anti-epileptic medications, and occur several times a day. Anti CASPR2 presents as Morvan syndrome, a rare phenotype with peripheral nerve hyperexcitability, autonomic instability, and encephalopathy. Other immune-mediated diseases might co-exist.

3. Anti -AMPA-receptor

Anti-alpha amino 3-hydroxy 5-methyl -4-isoxazole propionic acid receptor. Middle-aged females are more affected. Subacute confusion, memory impairment, and psychiatric features. 70% have tumor association. Antibody targets GluR1/2 subunit of AMPAR. Hypothyroidism, diabetes, and stiff person syndrome are associations. Medial temporal signal changes and lymphocyte-dominant CSF are seen.

4. DP PX (a potassium channel protein)

Antibody to Dipeptidyl- peptidase-like protein-6. affects middle-aged persons. Present with Diarrhoea, neuropsychiatric syndromes, myoclonus, tremor, and seizures. ataxia, trunk stiffness and hyperekplexia can occur.

5. Anti GABA -A encephalitis

Present as status epilepticus or Epilepsiapartialis continua. Any age but male dominant. Cellular CSF, increased proteins, OCB band, and abnormal MRI showing multifocal cortical and subcortical T2 and FLAIR changes. Tumour association is less common. Autoantibody to TPO and GAD can be seen.

6. Anti GABA -B encephalitis

50% have small cell lung tumors. Both genders were affected. Memory loss, confusion, seizures, and opsoclonus myoclonus are seen. Medial temporal signal changes are seen in MRI**.**

7. Anti igLON5

REM &NREM sleep disturbance, sleep apnea, poor response to treatment. EEG, MRI, CSF non-contributory.

DA encephalitis

Dopamine 2 receptor encephalitis presents as parkinsonism.

Myelin oligodendrocyte glycoprotein antibody syndrome.

MOG is a minor component of myelin seen on the surface of the myelin sheath. It can bind compliments. The diseases caused belong to a spectrum of NMOSD, ADEM, multiphasic disseminated encephalomyelitis, Recurrent or Bilateral optic neuritis, and unspecified focal cortical disease. Classical MOG produces anterior optic nerve, Conus pathology but NMOSD posterior visual pathway and long segment spinal cord. The cortical disease presents as seizures, behavioral problems, and the oedematous cortex.

Both monophasic and relapsing courses can occur. 50% of monophasic ADEM and almost 100% of multiphasic are MOG positive. Classical MOG lacks a progressive course and is highly steroid responsive start with 500 mg to 1000 mg intravenous for 3 to 5 days followed by oral 0.5 to 0.75 mg /kg for six months and tapered fast. If it still remains, a positive longer period of immunosuppression is considered. (9), (10). lymphocytes up to 100 to 300, and oligoclonal bands in CSF can occur. For children, 20 to 30 mg/kg a day for five days and tapered.

Other options are IVIg 2g/kg and subsequent monthly doses of 1g/kg/infusion, mycophenolate, azathioprine, methotrexate at adequate doses for weight, or Rituximab. If relapse occurs in Two weeks and six months after treatment. It is considered a failure. A 'repopulation relapse' was a relapse associated with B-cell repopulation (CD19 count ≥10×106 cells/L). (15)

mGluR5 Encephalitis

Memory Loss, Confusion. It can be associated with Hodgkin's lymphoma.

Neurexin-3a

Decreases synaptic function. Confusion, seizures, Encephalitis.

NMOSD

It is a more disabling anti-neuronal antibody-mediated disease than classical MOG and can be either AQP4 antibody positive for NR1,11 subunit of the receptor or can be negative. The clinical features are attacked more than one site, optic nerve, spinal cord, area postrema, brain stem as well as psychosis, seizures, movement disorder and/or autonomic instability, features of narcolepsy, and diencephalic features. Some of the NMO-negative patients can show MOG positive. Some show LETM (Longitudinally extensive transverse myelitis), Optic neuritis, multiple sites, and extensive disease. Adults often show neuropsychiatric features like anxiety, agitation, paranoia, severe cardiac dysrhythmia, and visual or auditory hallucinations .relapses are common and cause severe disability. Both cellular and humoral immunity involving T-cells, B-cells, aquaporin - 4IgG, Proinflammatory cytokines, and complement activation products happen. CSF shows lymphocytic dominance. Compliment blocker Eculizumab protects against damage to complement complexes that damage astrocytes and neurons. PREVENT trial focusing on time to relapse recommends Eculizumab. The patients need to be vaccinated against meningococcal infection. C5 convertase blocker ravulizumab, autoantigen specific aquaporumob, Proteosome inhibitor bortezomib, telitacicept, cyclophilin ligand TACI Fc fusion protein depriving B cells of activation are newer drugs.

Hashimoto encephalopathy

Fluctuating subacute confessional state. Myoclonus, seizures, Ataxia, and extrapyramidal features. Anti thyroglobulin or anti thyroperoxidase antibody is elevated in a euthyroidpatient. EEG is abnormal with slow waves, focal or generalized epileptic discharges, and CJD-like features. MRI can show white matter changes (figure 2)

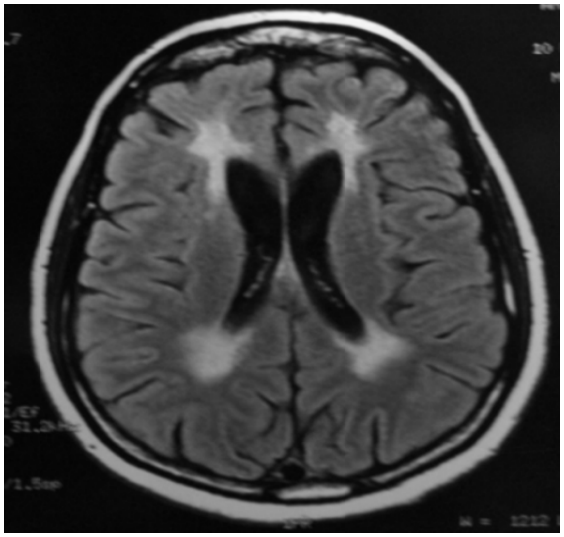

Figure 2: *White matter changes in Hashimoto encephalitis*

SLE & Wegners

Headache, psychosis, aseptic meningitis, depression, dementia, and stroke-like episodes occur. Antibody-mediated neuronal injury and

vascular compromise due to antiphospholipid syndrome occur. (figure 3)

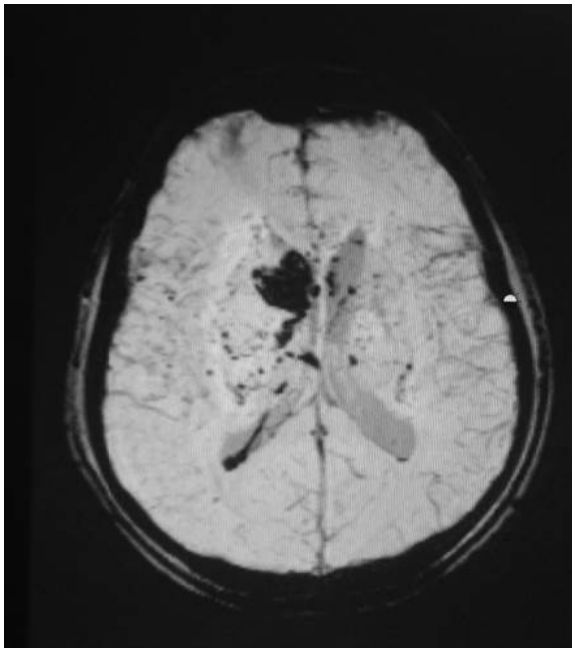

Figure 3*: Patient with SLE vasculitis*

Immune-mediated seronegative syndromes

Behcets disease causes uveitis, orogenital ulcers, aseptic meningitis, and T2 changes in the mesial temporal region, thalamus, and basal ganglia are seen. Coeliac disease is characterized by enteropathy and antibody to gluten. Sarcoid is a multisystem granulomatous disease. Pachymeningitis, cognitive dysfunction, and skin, eye, and lung involvement are seen. It can show white matter changes and mass lesions. Primary CNS Vasculitis presents with dementia, headache, focal deficits, multiple microbleeds, cerebral angiogram, leptomeningeal, and brain biopsy is diagnostic.

Diagnosis is made when all four of the following are present. 1. Rapid progression less than three months with working memory impairment and neuropsychiatric features. 2. exclusion of well-defined autoimmune conditions. 3. absence of antibodies in CSF and serum with MRI suggestive of autoimmune Encephalitis's Pleocytosis, OCB, elevated IgG index, brain biopsy when possible. 4. Reasonable exclusion of alternative causes.

clippers

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids. Recently described entity and causes peppering of pons radiologically due to curvilinear and punctate gadolinium enhancement. As described in 2010 by Pittock, neither pathogenesis nor any specific markers were identified. It is responsive to the early introduction of steroids.

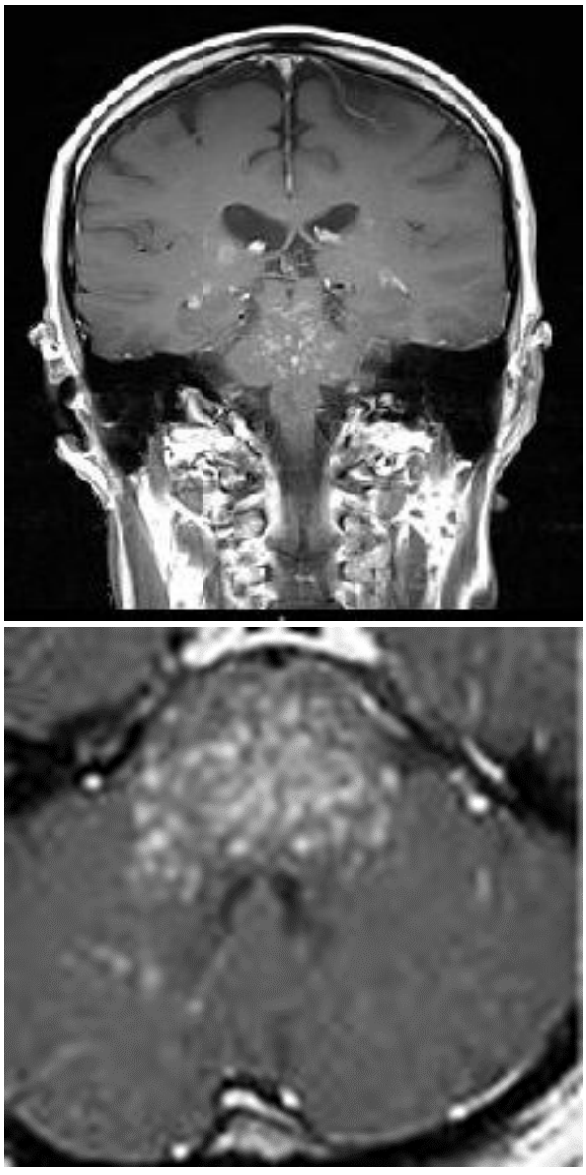

Figure 4*: Clippers syndrome MRI*

Gait ataxia, diplopia, dysarthria, facial sensory features, swallowing defect, dizziness, spasticity, and pseudobulbar affect are common. It is a diagnosis of exclusion. CSF shows a variable

picture. There is T cell infiltration in perivascular regions. The CD4 T cells noted in CLIPPERS suggest a major histocompatibility complex (MHC) class II-restricted antigen presentation involving perivenous regions.

MRI shows punctate and curvilinear enhancing lesions in Pons, Peduncles, Cerebellum, and occasional extension to the hindbrain. A very good response to steroids is seen, and to prevent a recurrence, long-term treatment, steroids with 2nd line immunotherapy is indicated. (16) (figure4)

Bickerstaff's brainstem encephalitis

Subacute onset, less than four weeks, altered consciousness, Ataxia and symmetrical, ophthalmoparesis preceded by infectious, has a monophasic course, pupillary abnormalities, Facial Palsy, Babinski's sign, and bulbar palsy are seen. And positive IgG anti-GQ1b antibody.

Amphiphysin

Rigidity, spasms, confusion, and Stiff-person, can be associated with breast cancer.

mGluR1 G

Presents as cerebellar Ataxia. Also, basal ganglia can be affected.

Susac's syndrome

Autoimmune vasculopathy affects the Brain, Ear, and Retina. Branch retinal artery occlusion and snowball-like lesions in carpus callosum located centrally within the fiber tracts without callosal atrophy. Synonyms are "SECRET syndrome" (Small Infarctions of Cochlear, Retinal, and Encephalic Tissue) or "RED-M" (Microangiopathy with Retinopathy, Encephalopathy, and Deafness). Seen in females 20 to 30 years. Clinical features include memory impairment, confusion, behavioral abnormality, Ataxia, dysarthria, paranoid psychosis, occasional mutism, and headaches.

Paraneoplastic limbic Encephalitis – antibody against intracellular proteins

Recognized about 50 years ago. Acute or subacute development of dementia, parkinsonism, cerebellar signs, encephalopathy, and family history of cancer increases the need for a search. Limbic and brainstem encephalitis is seen in 1/3 of patients. Autonomic dysfunction presenting as postural hypotension, gastropathy, bladder, bowel dysfunction, Cardiac dysrhythmias, and respiratory failure is not uncommon. There are signal changes in limbic and temporal regions that do not enhance.

Tumour association

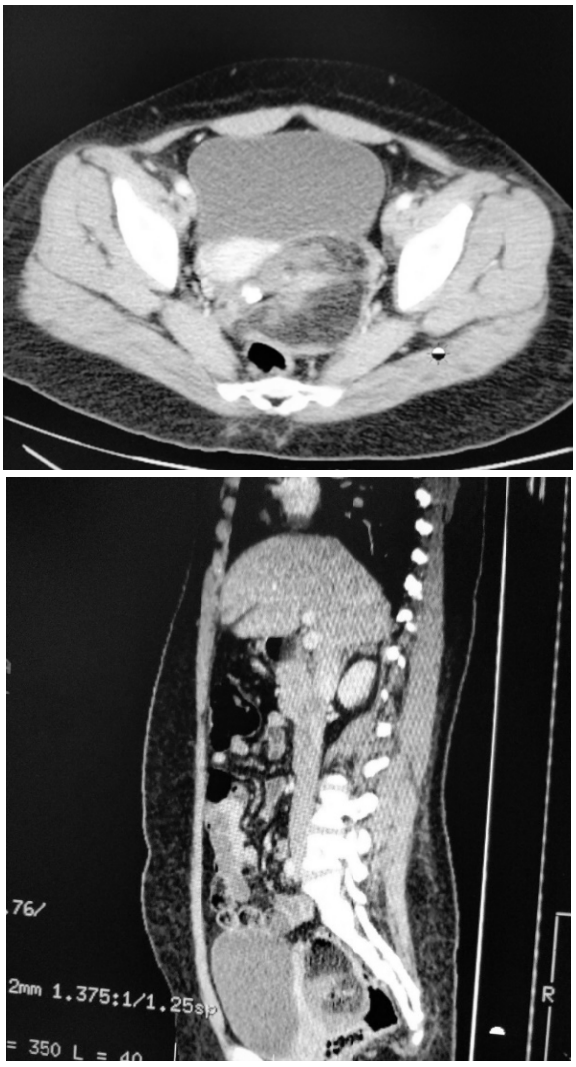

Figure 5*: Ovarian teratoma in our patient with NMDAR encephalitis*

NMDA receptor-ovarian or mediastin alteratoma. AMPA-lung, breast, thymus. Hu-small cell lung cancer, neuroendocrine tumors. Yo-ovary and breast. CV2/CRMP5-SCLC, Thymus. Risclc,

breast, ovary, Ma2-testes, breast, lung, stomach. Amphiphysin-SCLC, breast. SCLC, Non-SCLC, LG11-Thymus, Thyroid, lung, kidney. Caspr2-thymus. GABA-B-SCLC, GABA A-Thymus, myeloma, lymphoma. Mglu R5-Hodgkins, DPPT -?, Glycine receptor-thymus, breast, lymphoma. (Figure 5)

Seronegative Encephalitis

A group of patients has noninfective encephalopathy with no antibody positivity. They could be due to unknown antibodies if other features are supported.

Autoimmune Encephalitis in children.

One of the most common causes of pediatricencephalopathies. Common triggers are vaccinations, infections including HSV, and mass lesions. Antibodies against intracellular neuronal antigens, as well as surface or synaptic antigens, are seen.

Surface antigens mediate responses via antibody / complement-mediated immune response. Behavioral features, autonomic dysfunction, hypoventilation, seizures, movement disorders, sleep changes, and hemiplegia are features antibodies against IgG class G1, which binds the extracellular domain of the Glu1 subunit of NMDAR is the commonest antiglycan receptor antibody encephalitis occurs due to activation of the postsynaptic glycine receptor. α1 subunit of GlyR causes encephalomyelitis, myoclonus, and stiff person syndrome. Gamma-aminobutyric acid type A (GABAA) presents as status epilepticus. Anti-gamma-aminobutyric acid type B receptor encephalitis acts via K channels and presents with limbic symptoms and seizures. Autoantibodies are targeting the glutamate receptor 1 (GluR1) or GluR2 subunits of the α - amino - 3 - hydroxy - 5- methyl - 4 - isoxazole propionic acid receptor (AMPAR) present as a limbic syndrome. Anti-dopamine D2 receptor encephalitis is involved in Sydenham's chorea. Ophelia syndrome is limbic Encephalitis with Hodgkin's disease due to antibodies against the metabotropic GluR5.

Autoantibodies Targeting Intracellular Antigens

T-cell-mediated neuronal cytotoxicity. They are poorly responsive to treatment and therefore carry a poor outcome. Anti-Hu encephalitis presents as limbic Encephalitis. Anti-Ma2 Encephalitis is very rare and presents as the subacute onset of behavioral changes, focal seizures, speech disturbance, and dystonia. Anti-glutamic acid decarboxylase encephalitis presents as a stiff-man syndrome, Ataxia, epilepsies, limbic Encephalitis, and type 1 diabetes, intellectual and memory decline, developmental regression.

Outcome studies.

Autoimmune Encephalitis is a treatable disease with variable course and outcome. Type of antibody, time of treatment initiation, and other co-morbidities all determine the outcome. Recovery can happen in months to years. There is a role for neurologists, psychiatrists, occupational therapists, and speech pathologists in management. Long-term sequelae are not uncommon.

Treatment

Early diagnosis is important for a good outcome. No clinical trials have assessed the optimal treatment for AE. High-dose methylprednisolone 30 mg/kg/day, up to 1 g daily, for 3–5 days, with IVIg (2 g/kg divided over 2–5 days). Steroids are then tapered using 1–2 mg/kg/day orally over 12 weeks. If no response plasma 3–5 exchanges over ten days is done.

In Tumor-associated patients, the tumor should be removed. Steroids, plasmapheresis, and IVIg form first-line treatment. Shows improvement in 4 weeks and good recovery in 24 months. Those showing no response are given Rituxumob 375 mg/m2 every week for 4weeks or Cyclophosphamide 750 mg/m2 monthly. However, we in our center give for at least six months of intensive therapy with steroids, plasmapheresis, and one second-line drug, usually Azothioprim. Based on the response, clinically and

lab-based treatment is prolonged for up to 2 years though the recommendations for chronic therapy are to be based on the risk of recurrence. Intrathecal methotrexate is useful in pediatric cases of anti-NMDAR Encephalitis.

Each patient, however, needs individualized planning. NMDA encephalitis patients are reported to have a 25 % recurrence rate. Tumour removed when present. Then acute treatment consisted of pulse steroid and after eight days if response inadequate intravenous immunoglobulin) and second-line therapies plasma exchange vs. Rituximab + cyclophospha-mide. Though recommendations for chronic therapy are poor chronic therapy reduces recurrence for six months to two years with steroids, Rituximab, Mycophenolate, and IVIG. (17, 18)

Diagnostic dilemmas

Differential diagnosis involves primary psychiatric conditions, infections, metabolic and rapid presentation of degenerations.

Treatment

Treatment options recommendations reported are inconsistent. Both symptoms are modified, and disease-modifying treatments are indicated. Good responses are described with combination therapy of steroid and IVIG, and or plasmapheresis. 2 weeks to 24 months is needed for recovery. If the response is poor Rituximab, cyclophosphamide started, of course, with a higher risk of side effects. Expert management of seizures, psychosis, autonomic problems, and metabolic complications is required. Other drugs like bortezomib are used in special situations. Tumors are removed whenever identified. The outcome is better than infections, and hence a high degree of suspicion is needed.

Rituximab

An anticancer drug acts by complement-mediated cytotoxicity (CMC), antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity, complement-dependent cellular cytotoxicity, antibody-dependent cellular cytotoxicity, and induction of apoptosis. The usual dose of 375 mg/m2 once weekly for four weeks. Infusion-related reactions are not uncommon. Mild to moderate flu-like symptoms such as fever, chills, and rigors occur in most patients during their first infusion of Rituximab. When initiating treatment, given at 50 mg/h for the first 30 minutes, increased to 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h. Later the initial infusion rate is 100 mg/h, which is increased by 100 mg/h increments at 30-minute intervals to a maximum of 400 mg/h.

Treatment failure

Relapse occurring between 2 weeks and six months of Rituzumab is considered a failure.

A 'repopulation relapse' was a relapse associated with B-cell repopulation (CD19 count ≥10×106 cells/L).

Therapy with steroid and IVIG, Rituximab, cyclophosphamide, CD20 monoclonal antibody, or plasmapheresis are given in combination based on severity and response to treatment. Chronic treatment is given to all cases for at least six months, but the choice and duration of therapy are decided on several factors like fertility, tumor induction, risk of relapse, etc.

Conclusion

Autoimmune Encephalitis should be considered an important differential diagnosis in all probable situations. Antibody testing should be considered whenever indicated. Important to remember that laboratory data can sometimes be non-specific.

Acknowledgment

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