ANTI-NMDA-RECEPTOR ENCEPHALITIS IN A YOUNG WOMEN: A DIAGNOSTIC CHALLENGE

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ABSTRACT

A 42-year-old women is admitted in the Psychiatric Department with signs of acute psychosis. She had orolinguofacial dyskinesias, episodes of bilateral rigidity, oculocephalogyric crisis and becomes stuporous. The cerebral MRI highlighted two supratentorial demielination lesions. The CSF examination shows clear CSF with moderate pleocitosis and the predominance lymphocyte. Viral and bacterial cultures were negative. The patient is transferred to our Department of Neurology after 5 days, and runs a fever. Also, orolinguofacial dyskinesias, hypersalivation, puppet's eye syndrome, swallowing disorders, bilateral jerks osteotendinous reflexes, and coma state (GCS=5) are present. A second cerebral MRI was performed, which suggested two hypersignal lesions, T2, FLAIR and T1 hyposignal present, with no diffusion restriction, one being 0.9 cm, situated subcortically and to the right, the other of 0.5 cm being located on the left subcortical parietal, without gadolinium enhancement. The native pelvic CT scan marked out a 4.9 cm left annex cyst present. Anti-NMDAR antibodies were present in the CSF. As the patient was comatose, an interventional genital procedure is contraindicated. The patient was given iv Immunoglobulis, Methylprednisolone, Cyclophosphamide, anticonvulsives, and large spectrum antibiotics. She manifested multiple oculocephalogyric crisis, in both directions, bronchopneumonia, respiratory failure, requiring mechanical ventilatory support. The patient dies three weeks after the onset of the symptoms. The pathological examination revealed a left mature ovarian teratoma. The anti-NMDAR encephalitis is a life-threatening condition consisting of memory and psychiatric disorder, alteration of consciousness and hypoventilation, common associated with ovarian teratomas. The fast diagnosis and an early specific treatment can strongly influence the anti-NMDAR encephalitis's natural evolution.

Keywords: Anti-N-methyl-D-aspartate-receptor (NMDAR) encephalitis, autoimmune encephalitis, paraneoplastic syndrome, ovarian teratoma

INTRODUCTION

Encephalitis, an inflammatory process of the brain, often associated with neurological dysfunction, represents a common medical emergency. In case of misdiagnosing the appropriate etiology, the patient is at risk of important morbidity or even death (1-4).

Most often, the cause is infectious, mainly viral agents including herpes virus type 1, 2 and 6, varicella-zoster virus, EBV, rubella, mumps virus, measles virus (1,5).

However, autoimmune phenomena are being recognized as causes of encephalitis.

There have been described several types of autoimmune encephalitis: ADEM (acute disseminated encephalomyelitis) which is a post-viral condition, and several other types, according to a specific antibody which is found in blood. These conditions include: anti-LGI1 encephalitis (previously anti-voltage-gated potassium channel anti-VGKC antibody encephalitis), anti-N-methyl-D-aspartat receptor (anti-NMDAR) encephalitis, Hashimoto's encephalitis, Rasmussen encephalitis (2,3,6,7).

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CASE PRESENTATION

We present the case of a 42-year-old women without a history record, who enters the Brasov Clinical County Emergency Hospital with behavior disorders including anxiety, insomnia, confusion. The symptoms appeared suddently a few days before the hospitalization.

Because the symptoms strongly suggested a psychotic disorder, the patient is hospitalized in the Psychiatric Department. When she reached the examination room, the patient was hemodynamically stable, apyretic, BP 110/65 mm Hg, and she had heart rate 64 bpm.

During the hospitalization, the patient becomes nervous, showing signs of grandness and delirium which alternate with periods when the patient becomes isolated and anxious.

Progressively, her state of mind alters and she becomes stuporous for which she is transferred to the ICU Department. She has been suspected for drug overdose (tested Benzodiazepine positive) and thus she is being administered Flumazenil to diminish the control of the sedatives effect. The patient manifested orolingual and facial dyskinesias, and episodes of bilateral rigidity and oculocephalogyric crisis.

The first cerebral CT scan exam showed no suggestive changes, which is why the investigations continued.

The CSF examination shows clear CSF with moderate pleocitosis and the predominance lymphocyte, a normal protein and glucose levels. Viral and bacterial cultures studies through PCR tested negative.

The cerebral MRI that was taken in Brasov Clinical County Emergency Hospital highlighted two supratentorial demielinating lesions, the first being a 8 mm lesion situated frontaly and to the right and the second, a 7 mm lesion located in the left side of the fronto-parietal region, also chronic inflammatory modifications involving the thickening of the sphenoid sinuses mucosa.

Thus, Rasmussen encephalitis is excluded because the pathologic process involves only one cerebral hemisphere which sufferes atrophy.

Immunological samples were taken, which showed normal to colagenosis. Blood samples tested negative for HIV, Borrelia and VDRL. Because of the suspicion that Hashimoto¢s encephalitis is present, samples have been gathered to analyze the thyroid function. There is only a slight free T3 decrease, with the ATPO's antibodies within the normal parameters.

A treatment of 1 g of Methylprednisolone/day is established.

Another diagnostic that was brought into discussion was the possibility of autoimmune encephalitis with anti-NMDA receptor (NMDAR) antibodies or anti VGKC antibodies and blood was taken to determine these antibodies.

Approximately five days after the first signs of the disease started manifesting themselves, the patient is transferred to the Department of Neurology, Colentina Clinical Hospital, to continue the investigation and receive proper treatment.

When the patient was admitted, she showed a mediocre generat state, she ran a fever of 38.9 degrees Celsius, with BP 110/60 mm Hg, HR 62 bpm.

When the neurological exam is take, the puppet's eye syndrome is present, there are swallowing disorders towards the ingestion of liquids and solids, the velopalatine and pharingian reflexes are diminished, bilateral jerks osteotendinous reflexes, sphincter incontinence is present, and coma state (GCS = 5 points). During the time when the period of admittance, the patient again manifested orolingual and facial dyskinesias and hypersalivation.

The EEG shows a diffuse slowing in range of 6-7 Hz/s.

The ECG shows no signal of conduction and repolarization irregularities.

The second cerebral MRI has suggested two hypersignal lesions, T2, FLAIR and T1 hyposignal present, with no diffusion restriction, one being 0.9 cm big, situated subcortically and to the right, the other of 0.5 cm being located on the left subcortical parietal side. The lesions described have no gadolinium enhancement.

A fine abnormal vascular structure in the right cerebellum is draining the transverse/angyomic venous sinus. There are no pathological iv substance contrast enhancement. There is no evidence of thrombosis of the venous sinuses (there is a slight left transverse sinus hyperplasia (Fig. 1).

An ovarian teratoma screening is mandatory in the case of female patients with anti-NMDAR encephalitis, consisting of: pelvic CT scan, MRI, and transvaginal ultrasound and the dosage of tumoral CA125, b-HCG, α-fetoprotein, testosterone markers (which often teste negative in lots of patients).

The native pelvic and abdominal CT scan marked out an uterus which was increased in size, but had smooth outlines.

There is a 4.9 cm left annex cyst present, with no adenopathic nodules and no ascitic liquid (Fig. 2).

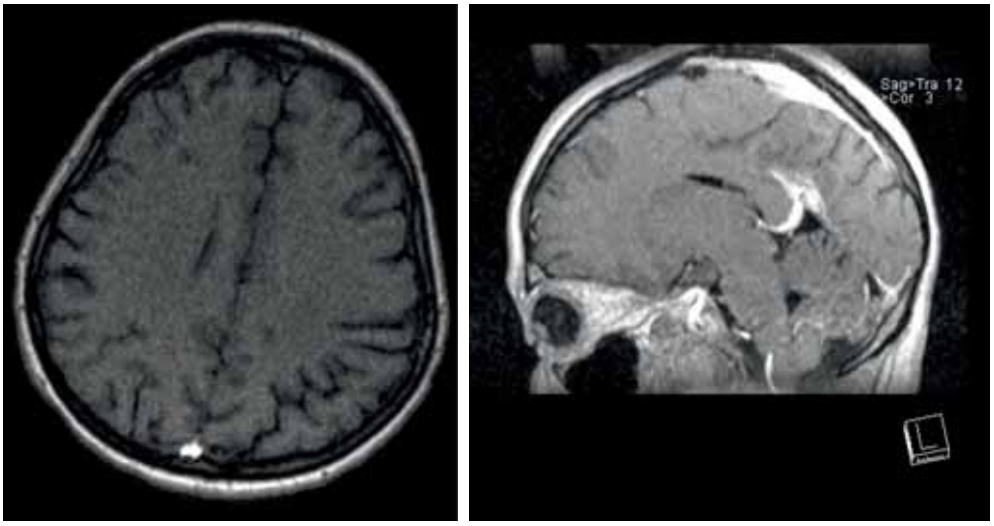

FIGURE 1. *Cerebral MRI – two hypersignal lesions, T2, FLAIR and T1 hyposignal present, with no diffusion restriction, one of 0.9 cm big, situated subcortically and to the right, the other of 0.5 cm being located on the left subcortical parietal side. The lesions described have no gadolinium enhancement. A fine abnormal vascular structure in the right cerebellum is draining the transverse/angyomic venous sinus. There are no pathological iv substance contrast enhancement. There is no evidence of thrombosis of the venous sinuses (a slight left transverse sinus hyperplasia)*

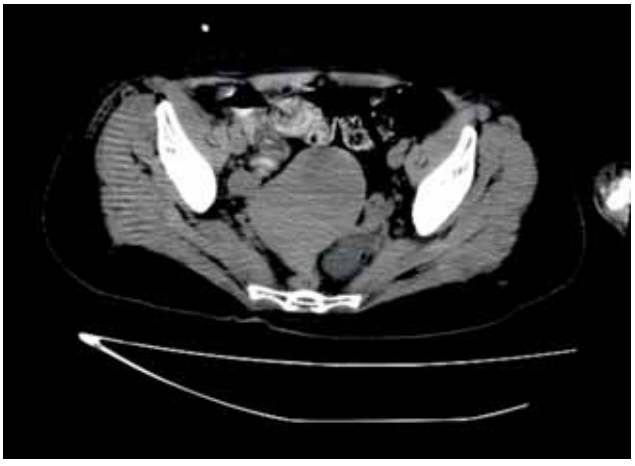

FIGURE 2. *Native pelvic and abdominal CT – uterus increased in size, with smooth outlines. There is a 4.9 cm left annex cyst present, with no adenopathic nodules and no ascitic liquid*

Seric values of CA125 and α-fetoprotein were in normal ranges.

Anti-NMDAR antibodies were present in the CSF.

Anti-VGKC antibodies were absent in the CSF.

Because of the presence of anti-NMDAR antibodies is associated with ovarian teratoma, an interventional and exploratory genital procedure would have been necessary, but as the patient was comatose, that is contraindicated.

The patient was given iv Immunoglobulis treatment (0.4 g/kg/day/5 days) associated with Methylprednisolone (1 g/day/5 days) and immunosuppressors (Cyclophosphamide 0.2 g/d/5 days). The plasma exchange is rarely indicated in young uncooperative and unstable patients.

A metabolic and hydroelectrolytic rebalancing symptomatic treatment is administered which also contains anticonvulsivants (initial loading with Phenhydan and afterwards Levetiracetam 3000 mg/d and Clonazepam 8 mg/d) and large spectrum antibiotics.

During the process, the patient manifested multiple oculocephalogyric crisis, which were directioned both to the right and to the left, first rigidity through decortications and afterwards through decerebration, bronchopneumonia, followed by respiratory failure, requiring orotracheal intubation and mechanical ventilatory support.

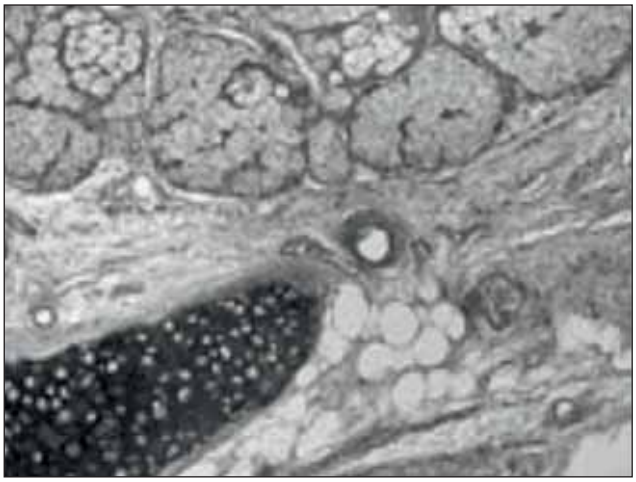

FIGURE 3. *Mature ovarian teratoma with sebaceous glands and cartilage H-E, OM x 200*

The patient dies three weeks after the onset of the symptoms, despite adequate treatment.

The pathological examination revealed a left mature ovarian teratoma with sebaceous glands and cartilage (Fig. 3).

DISCUSSION

The classic presentation of autoimmune encephalitis is encephalopathy with diffuse or focal neurologic symptoms, including behavioural and personality changes, decreased level of consciousness, neck pain, stiffness, photophobia, lethargy, seizures (either focal or generalized), acute confusion or amnestic state, flaccid paresis (8).

In ADEM, the illness usually begins with less-specific symptoms such as fever, headache, stiff neck, vomiting and anorexia. These are rapidly followed by depression of consciousness in which the patient may become confused and occasionally comatose. Neurological features which may be detected include visual deterioration, clumsiness of the arms and legs, paralysis down one side and seizures. The duration of these symptoms is variable. Some cases last a few weeks to a month, while other fatal cases have a rapid progressive course over a number of days. The clinical sign that correlates mosst closely with prognosis is the level of consciousness

At the onset of anti-NMDAR encephalitis the most distinctive features include prominent psychiatric symptoms, seizures, confusion and memory loss. Patient will sometimes show bizzare and often rather disturbing behaviors. Typically 10 to 20 days later, patients develop a movement dosorder, variations in blood pressure, heart rate and temperature and may become less conscious. The movement disorder often consists of continuous writhing and twitching of face and limbs but can also be a generalised slowing-domn of movements.

In limbic encephalitis, men are affected about twice as often as women. Initially, family members often notice that their relative becomes forgetful, drowsy and withdrown. Patients can also develop mood disorders (like depression) or bizarre thoughts and behaviours.

In addition, seizures frequently occur. These may take the form of brief absences when patients glaze over for a few secons (also called temporal lobe epilepsy) or full blown arm and leg jerking which can be very disturbing for observers (also known as generalized seizures) – this is an important feature and highly suggestive of VGKC antibodies.

The clinical presentation of Hashimoto¢s encephalitis occurs over a few weeks or months and often includes drowsiness, imbalance, stroke-like episodes, psychiatric disturbances, jerky movements (some of which may be seizures) and sometimes coma.

Rasmussen encephalitis is characterised mainly by intractable seizures, progressive hemiparesis, and unilateral hemispheric atrophy (3).

The outcome is variable depending on the type of encephalitis, some may improve rapidly after treatment, while others take time to fully recover, if they recover at all.

Anti-NMDAR encephalitis

In 2005 a syndrome consisting of memory and psychiatric disorderd, the alteration of consciousness and hypoventilation in young women which had ovarian teratomas was described in medical literature. Specific autoantibodies against the N-methyl-D-aspartat receptor (NMDAR) are detected in these patients. In 2007 this affection gets the name anti-N-methyl-D-aspartat-receptor (NMDAR) encephalitis (9).

Incidence and epidemiology

Anti-NMDAR encephalitis accounts for only 1% of all encephalitis that are initially thought be of unknown etiology (10).

The results of California Encephalitis Project revealed that the condition had a higher incidence than its individual viral counterparts in patients under 30 years (11,12).

Signs and symptoms

The presence and order of symptoms is variable, with a progressive course:

1. A prodromal phase of nonspecific viral-like symptoms (fever, headache, nausea, vomiting, diarrhea, or upper respiratory tract symptoms). Whithin a few days (less than 2 weeks) the next stage appears

2. Psychiatric disturbances: anxiety, insomnia, fear, grandiose delusions, hyperreliogisity, schizophrenic-like manifestations (hallucinations, visions, suicidal ideation, mania and/or paranoia); social withdrawal and stereotypical behavior are sometimes seen; disintegration of language, from reduction of verbal output and echolalia (usually with echopraxia) to frank mutism, is frequent and cannot be atributed to cortical aphasia.

This is usually the phase that patients are admitted to hospital (13-26).

3. Memory impairment – in particular anterograde amnesia (14).

4. Dyskinesias (especially orolinguofacial, fish-mouthing, grimacing, masticatoy-like movements, and forceful jaw opening and closing, limb and trunk choreoathetosis, elaborate leg and arm motions, dystonia, rigidity, opisthotonus), catatonia, oculomotor symptoms (oculogyric crisis, inverse ocular bobbing), myoclonus and seizures (often tonic-clonic but not associated with epileptiform activity as assessed by electroencephalography); in rare cases opsoclonus-myoclonus syndrome may be at presentation (13-15, 27-29).

It is suggested that interruption of forebrain corticostriatal inputs by anti-NMDA receptor antibodies removes tonic inhibition of brainstem pattern generators realising primitive patterns of bulbar and limb movement (30).

5. Loss of responsiveness, decrease of responsiveness that can alternate between agitation, catatonia and coma, in some cases odd reaction like resisting eye opening while not responding to pain (dissociative responses) with proposed disgnostic of malingering or psychogenic reactions, low Glasgow Coma Scale.

6. Hypoventilation/central respiratory depression (may require ICU admission) (13,31), unrelated to seizures or antiepileptic medication, the patients require prolonged ventilatory support (9,16,32-34).

7. Autonomic instability (hyperthermia, tachycardia, in rare cases causing bradycardia requiring temporary peacemaker insertion, fluctuating blood pressure, hypersalivation, urinary incontinence, erectile dysfunction) (11,13,35).

The nonspecific onset can mask the real etiology, and can easily be mistaken for a psychiatric disease, as it happend in our case. Young women, with psychosis, memory and behaviour disorders, convulsive crisis, with the alteration of the state of consciousness leading to a coma, which have associated involuntary, abnormal movements, should lead us to diagnose them with encephalitis. Follow-up with laboratory and imaging investigations may solve the case. The faster the correct treatment is given, the better the evolution will be (36,70,88).

Rarely, in patients with extensive myelitis who are seronegative for anti-AQP4 antibodies, and after other clinical causes have been excluded, the hypothesis of atypical anti-NMDAR antibodies encephalitis should be also be considered (37).

The disease can both occur in children and adults

Children can show signs of hyperactivity, irritability, convulsive crisis, language disorders and only behavior disorders (38-42).

Pathophysiology

The presence of antibodies in the CSF

The autoantibodies target NMDA receptors in the brain. These are produced by cross reactivity with NMDA receptors in the teratoma; these tumors contain many different cell types, including brain cells, and thus present a window in which a breakdown in immunological tolerance can occur. Causal factors in tumor-negative patients are largely unknown.

Two possible mechanisms are described:

1. Passive access involves the diffusion of antibodies from the blood across a pathologically disrupted blood-brain-barier (BBB).

2. Intrathecal production of antibodies is the second mechanism. This fact is proved by the existence of a high level of antibodies in the CSF in patients with this disease and by the good therapeutical response to Cyclophosphamide and Rituximab, drugs used as second therapeutical line in patients where the first line has failed; they act by destroying excess antibody producing cells in the thecal space (31).

The binding of antibodies to NMDA receptors

In the CSF the IgG antibodies bind to the NR1 subunit (25-380 amino-acids residues) of the NMDA receptor; the NR2B subunit seems to be not necessarily involved, but recent studies have demonstrated that it was identified in the normal ovary and in certain pathological conditions it may cause an antigen-antibody reaction (43).

There are three possible methods in which neuronal damage occurs:

1. A reduction in the density of NMDA receptors on the post synaptic knob, due to receptor internalisation once the antibody has bound. The antibodies of patients with anti-NMDAR encephalitis cause a specific, titer-dependent, and reversible loss of NMDARs (44).

2. The direct antagonism of the NMDA receptor by the antibody, similar to action of typical pharmacological blockers of the receptor, such as phencyclidine and ketamine (45).

3. The recruitment of the complement cascade via the classical pathway (antibody-antigen interaction). Membrane attack complex (MAC) is one of the end products of this cascade and can insert into neurons as a molecular barrel, allowing water to enter. The cell subsequently lyses. This mechanism is unlikely as it causess cell to die, which is inconsistent with current evidence (46).

The selective and reversible decrease in NMDAR surface density and synaptic localization cau-

ses reduction in GABA release from pre-synaptic neurons that subsequently results in increased glutamate release, dopamine dysregulation and excitotoxicity leading to classical anti-NMDAR encephalitis features (47).

Experimentally, in a mouse strain in which essential NR1 subunit of the NMDAR was selectively eliminated in 40-50% of cortical and hippocampal interneurons in early postnatal development, distinct schizophrenia-related symptoms emerged after adolescence, secondary to cortical GABAergic dysfunction (48).

NMDAR are the major mediators of excitotoxicity and their dysfunction has been associated with schizophrenia (NMDAR hypofunction), epilepsy, and dementia (49).

IgG NR1 antibodies were not detected in patiens who met DSM-IV criteria for schizophrenia; NR1 IgG or IgA antibodies have been reported in many other disorders, without syndrome specificity, they can occur in patients with mild cognitive impairment and schizophrenia, among others (50-53).

Also, drugs interacting with this receptor (ketamine and phenylcyclidine) may result in paranoia, hallucinations, and dyskinesias (45).

Some authors found that in the anti-NMDAR brain biopsies there was a rarity of T-cell infiltrates as opposed to that found in paraneoplastic syndromes in which T-cells are predominant (54,55).

It is not known why the disease preferentially affects hippocampal NR1 subunits, when these can be found throughout the brain.

Brain necroptic examination showed extensive microgliosis, rare T-cell infiltrates, and neuronal degeneration predominantly involving, but not restricted, to the hippocampus (13).

Anti-NMDAR antibodies were observed also in 30% patients with herpes simplex encephalitis, suggesting secondary autoimmune mechanisms, such as generation of antibodies against neuronal cell surface antigens (56).

It is well known that peripheral nerve contain high amounts of NMDAR protein, which becomes phagocytosed after disintegration of the nerve in inflammatory neuropathies. Transport to lymphoid organs may then trigger a secondary immune response resulting in encephalitis in some cases (57).

Genetic vulnerability coupled with an antecedent viral infection may predispose some individuals to developing anti-NMDAR encephalitis. It has been proposed that a viral infection may trigger an inflammatory reponse that disrupts the BBB, allowing autoantibodies to enter the CNS; this may subsequenty allow antigen-specific T-cells to become involved in intrathecal production of antibodies to NMDARs that bind to subcortical neurons (58).

Investigations

CT and MRI of the brain with contrast are the initial investigations in an encephalitic syndrome.

The brain MRI is unremarkable in 50% cases, and in 50% cases T2 or FLAIR signal hyperintensity might be seen in the hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia and brainstem (14).

In rare cases with anti-NMDAR encephalitis the clinical symptoms oriented towards this disease, but the brain and spinal MRI images showed demyelinating lesions ADEM-like, suggesting an overlap between anti-NMDAR encephalitis and demyelinating diseases, potentially involving other immunological mechanisms (59).

The neuroimaging finding may differ from classic limbic encephalitis, combining MRI, FDG-PET, and SPECT only one third of the patients had the characteristic FLAIR or T2 medial temporal abnormalities seen in limbic encephalitis, the other two thirds of the patients had abnormalities in other areas of the CNS or normal MRI (16).

The clinic-radiologic dissociation seen in this disorder could be explained by investigation of structural and functional brain changes using a resting-state functional MRI, diffusion tensor imaging and voxel-based morphometry as well as conventional imaging and neuropsychologic testing. Anti-NMDA-receptor encephalitis is asociated with characteristic alterations of functional connectivity and widespread changes of white matter integrity despite normal findings in routine clinical MRI (60).

A striking correlation was observed between prehypoxic cerebral FDG-PET hypermetabolism in caudat nuclei and cerebellum and posthypoxic MRI changes (due to a seizure) in the same areas, suggesting increased susceptibility of these areas to hypoxia in anti-NMDAR encephalitis (61).

CSF examination with cell count, protein, glucose (and serum glucose), viral screen, acid-alcohol fast bacilli (AAFB) smear, bacterial and mycobacterial culture is necessary.

80% of patients with confirmed anti-NMDA encephalitis have abnormal CSF with the majority of these exhibiting a lymphocytic pleocytosis but over half also showing raised protein.

There may also be the presence of oligoclonal bands in the CSF (around 60%) (14).

An EEG and video-EEG recording is useful, over three quarters of patients had abnormal EEGs,

predominantly with generalized or frontotemporal slow or disorganized (delta-theta) activity in the absence of epileptic discharges (31,62).

An electroencephalogram pattern described as extreme delta brush was identified in 30% of patients with anti-NMDAR encephalitis. The presence of extreme delta brush was associated with a more prolonged hospitalization (63,64).

Some of the results from these investigations in both the case of infection and autoimmune encephalitis may overlap.

Blood screen for autoimmune antibodies: anti-NMDAR, anti-LGI1, anti-CASPR2, anti-AMPA, anti-GABA, vasculitic screen must be performed.

The anti-NMDAR antibodies can be identified both in serum and CSF, but never in serum alone (65).

If patients respond to treatment they have lower levels post-than pre-treatment (14,44,66).

Neoplasm screen especially if positive anti-NMDAR or paraneoplastic screen may be also performed (2).

Differential diagnosis

HSV encephalitis and other viral encephalitis should be excluded with appropriate testing.

Most autoimmune encephalitis cause psychiatric symptoms and CNS inflammatory abnormalities; however, MRI scan revealing hyperintensities involving medial temporal lobes are frequent in only two disorders: the paraneoplastic limbic encephalitis and anti-LGI1 encephalitis (anti-VGKC antibody encephalitis).

Other causes of autoimmune-related encephalopathies include systemic lupus erythematosus, antiphospholipid antibody syndrome, Sjogren's syndrome, and Hashimoto's encephalopathy.

The triad of alteration in mental status, rigidity, and dysautonomia can occur in the neuroleptic malignant syndrome, serotonin syndrome, or malignant catatonia. These conditions can all include muscle hyperactivity, hyperthermia, metabolic acidosis, rhabdomyolysis, elevated creatine kinase (CK), seizures and renal failure (67).

Neuroleptic malignant syndrome and serotonin syndrome can be confused with anti-NMDAR encephalitis as a result of the fact that most patients with the latter are initially seen in psychiatric centers and might receive neuroleptics or antidepressants (68).

Malignant catatonia is characterized by abrupt unresponsiveness, muteness, psychomotor changes, fever, and autonomic instability.

Malignant catatonia may be difficult to be distinguish from neuroleptic malignant syndrome, because both share hyperthermia and rigidity as defining characteristics. Muscle rigidity in malignant catatonia is characterized by more dystonic posturing, waxy flexibility, and stereotyped repetitive movements.

In neuroleptic malignant syndrome, serotonin syndrome, and lethal catatonia there are not inflammatory signs in the CSF.

Management and prognosis

Anti-NMDAR encephalitis is a disorders that appers to represent a new cathegory of sever, potentially lethal, but treatment-responsive paraneoplastic encephalitis (69).

Female patients with positive anti-NMDAR antibodies require compulsory ovarian teratoma exploration. Surgical removal together with qualified treatment suggest a good prognosis. Although oophorectomy is not recommended if the tumor screening is negative, any small cystic and persistent lesion of the ovary must be viewed with a high index of suspicion and its removal is recommended (6).

Patients whose tumor was diagnosed and treated within 4 month of neurological symptom development had better outcomes (full recovery or mild deficits) than those whose tomour was treated after 4 months of neurological symptom development or not treated, those without tumor, or these two groups combined (14).

Early tumor resection is the most important factor enabling prompt and full recovery from anti-NMDAR encephalitis (70,71).

Including a laparascopy with biopsy in cases with anti-NMDAR encephalitis and negative investigations for ovarian teratoma is very useful, leading to ovarectomy and clinical improvement (72).

There are no firm guideliness as to which kind of immune therapy should be used in these patients. However, immunotherapy should be started early while the screening of the tumor is conducted and without waiting for the results of the antibody determination (6).

First intention treatment consists of steroids to suppress the immune system, iv immunoglobulins and plasmapheresis to physically remove antibodies.

Second intention one includes Rituximab, a monoclonal antibody that targets the CD20 receptor on the surface of B cells, thus destroying the self-reactive B cells and Cyclophosphamide, an al-

kylating agent that cross-links DNA and is useful when other therapies have failed, or both as is highly recommended to patients with no tumours or with bilateral diagnosis. The sooner the treatment begins the better the evolution (6,13,14,17,31,35, 73-78,80).

Some authores recommended Rituximab (375 mg/m^2) initiation with the first dose of Cyclophosphamide (750 mg/m^2), Rituximab is continued every week for 4 weeks, while Cyclophosphamide is dosed every month until there are signs of significant clinical improvement and decreased serum and CSF titers of anti-NMDAR antibodies (14).

Recently, alemtuzumab was shown to enhance outcome, it is an anti-CD52 monoclonal antibody that affects memory B cells and T cells (1 mg/kg total dose of iv alemtuzumab associated with intrathecal admisitration of methotrexate). The rationale for this approach was to reduce peripheral memory B cells and T cells with alemtuzumab, which does not cross the BBB, and to eliminate inflammatory infiltrates in close contact to meninges with methotrexate, which does not penetrate the brain enough to reach the more distant intraparenchimal infiltrates (79).

For patients with no detectable tumors continued immunosuppression with azathioprine or mycophenolate should be considered, as these patients tend to experience relapses of symptoms; immunosuppression must be continued at least 1 year.

Perhaps for the patients who do not respond to first-line and second-line immunotherapies, the time has come to be bold; physicians should be aggressive in trating this specific subgroup of patients (52,91); inversely, in demyelinating forms and in inflammatory variants of anti-NMDAR antibodies encephalitis plasma exchange and IVIg are not effective (92).

The large number of events (patients achieving a good outcome) and prospective follow-up of many cases reported, provide level II-2 evidence of the usefulness of immunotherapy and tumor removal in anti-NMDAR encephalitis (73).

Periodic screening for ovarian teratomas in female patients over the age of 12 years with MRI of the abdomen and pelvis every 6 months for 4 years has been recommended.

Dopamine-receptor antagonists have been used for management of aggression, agitation, and hallucinations without significant improvement, and can in fact obscure an already-complex clinical picture. Potent D2 antagonists, (e.g. haloperidol) must be used judiciously, because they can intensify movement disorders (80).

Administration of Risperidone 2 mg/day for psychosis has a good clinical response (81). Mood stabilizers for emotional lability, benzodiazepines, other sedative hypnotics and histaminergic agents for insomnia are frequenly used.

Anticholinergic drugs are the most common used medications to treat dystonia, as well as carbidopa-levodopa for muscle rigidity (81).

In catatonia iv benzodiazepines can be administered at regular intervals. In malignant catatonia the patients become unresponsive to incresing dose of benzodiazepines.

Modified electroconvulsive therapy is effective for psychiatric symptoms in cases uncontrolled with medication due to their side effects (82-85). The mechanism of action of electroconvulsive therapy remains largely unclear. Still, in animal models it has been shown to upregulate NMDA receptors (86).

Seizures and epipeptic status are refractory to antiepileptic drugs and this may therefor lead to over-treatment (31).

Good clinical outcomes correlated with decreased NMDAR antibody level and were associated with early (< 40 days) administration of immunotherapies in non-paraneoplastic patients and earlier tumor removal in paraneoplastic patients (87, 88).

Nonpharmacological and multidisciplinary interventions are also useful.

In Fig. 4 is presented the algorithm for the diagnosis and treatment of autoimmune encephalitis.

Recovery from this condition is typically slow, it is a multistage process; the rate of severe morbidity and mortality is about 25% (13). More than 75% off patients have substantial recovery in inverse order of symptoms development and is associated with a decline of antibody levels (14).

A characteristic feature of patients who recover from anti-NMDAR encephalitis is a persisting amnesia of the entire process (13).

Social behavior anf executive function symptoms are usually the last to improve, and recover can be incomplete or delayed by many month (89).

The deterioration or partial recovery of a few patiens may reflect a more sustained disruprion or involvement of other critical epitopes of the NMDAR, or a secondary effect of the pathological seizures, leading to neuronal degeneration (9).

For the acute stage of the disease, many patients need to be hospitalizes for at least 3-4 month, followed by several months of physical and behavioral rehabilitation (90).

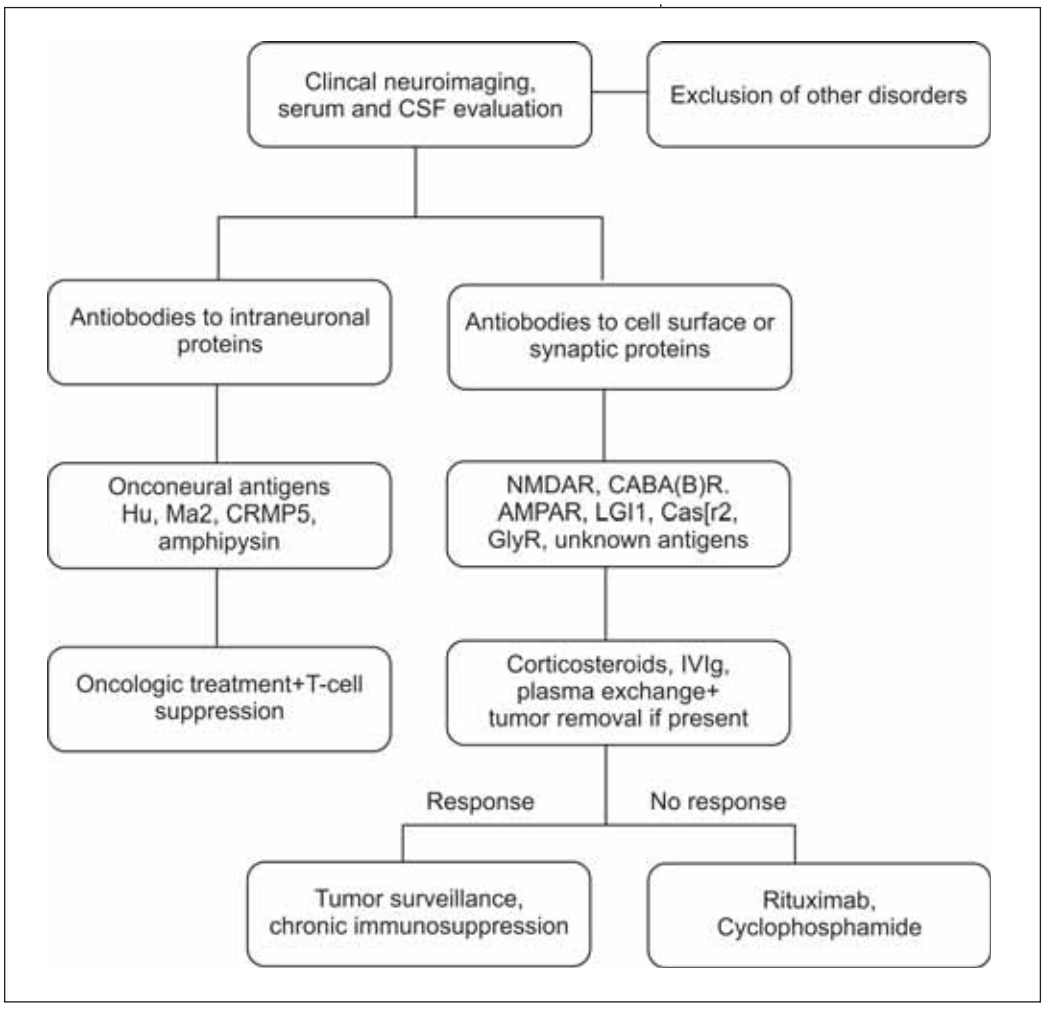

FIGURE 4. *Autoimmune encephalitis: diagnosis and treatment (46)*

In our case the course of anti-NMDAR antibodies encephalitis was fulminant with high severity of symptoms with low grade coma despite correct administration of the treatment.

It is the first case with anti-NMDAR encephalitis and ovarian teratoma published in Romania; other Romanian authors presented in a poster a similar case with full recovery (93).

CONCLUSIONS

The anti-NMDAR encephalitis is a life-threatening condition consisting of memory and psychiatric disorder, alteration of consciousness and hypoventilation, common associated with ovarian teratomas.

The acknowledgement of the symptoms, the fast diagnosis and an early specific treatment can strongly influence the anti-NMDAR antibodies encephalitis¢s natural evolution.

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