

Non-paraneoplastic Anti-NMDAR Encephalitis: First Confirmed Adult Case Report in Latvia

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Abstract: Anti-NMDAR (Anti-N-Methyl-D-aspartic acid) encephalitis is a rare autoimmune condition mainly affecting young women. It is associated with an underlying tumor in about 50% of reported cases. Antibodies directed against the GluN1 subunit of the NMDA receptor are responsible for the disease pathogenesis and their detection in the patient's serum and cerebrospinal fluid are required to make a definite diagnosis. Classical clinical presentation consists of flu-like symptoms, followed by psychiatric disturbances and impaired consciousness, epileptic seizures and movement disorders. During the past decade, it has become an emerging area of research and discussion as more than 1,000 cases have been reported since the first description of this specific disease entity in 2007. Despite a rather typical clinical course it is frequently diagnosed and treated with a delay up to many months. Overall prognosis tends to be favorable. However, it strongly depends on early diagnosis and rapid treatment initiation. While diagnostic criteria for probable and definite anti-NMDAR encephalitis have been proposed, there are no evidence based guidelines for specific treatment strategies. Glucocorticoids, plasma exchange and IVIG are generally used as 1st line treatment, in patients who do not respond, 2nd line treatment with Cyclophosphamide or Rituximab is used. We report a case of a confirmed non-paraneoplastic anti-NMDAR encephalitis with a rather classical manifestation in a Latvian woman who is first hospitalized in a psychiatric clinic then transferred to an ICU (intensive care unit), treated with glucocorticoids, plasma exchange and later Cyclophosphamide with a good outcome.

Key words: Anti-NMDAR encephalitis, non-paraneoplastic, psychosis, immunomodulatory therapy, Cyclophosphamide.

1. Introduction

Autoimmune conditions have become increasingly appreciated as a cause of encephalitis. Anti-NMDAR (Anti-N-Methyl-D-aspartic acid) encephalitis is the most common antibody mediated encephalitis accounting for about 4% of all encephalitides, though this is likely to be an underestimation [1, 2]. The clinical characteristics of NMDAR encephalitis in association with ovarian teratoma were first described in 2005, anti-NMDAR antibody relation to the particular disease entity was first described in 2007 [3, 4]. Since then the number of anti-NMDAR encephalitis case reports has progressively grown each year, up until now more than 1,000 cases of anti-NMDAR encephalitis have been described [5].

During this time, understanding of disease pathogenesis, clinical characteristics, tumor association and possible patient outcomes has considerably grown. While a noticeable female predominance is seen, as about 80 % of cases occur in women, this disease has been also identified in males [2]. Young adults are affected primarily in their third decade of life, however the disease also occurs in children and elderly. It is now known that anti-NMDAR encephalitis is not necessarily a paraneoplastic disorder. In about half of female patients no underlying malignancy is found, the proportion of paraneoplastic anti-NMDAR encephalitis is even smaller in male and children patient groups [2, 5]. Clinical criteria proposed by Graus et al. [6] in 2016 provide early diagnosis of anti-NMDAR encephalitis. Laboratory and instrumental data help in the diagnosis, however a

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noteworthy feature of anti-NMDAR encephalitis is that it is unlikely to have associated neuroimaging abnormalities on initial presentation (89%) or follow-up MR imaging of the brain (79%) [7]. A majority of anti-NMDAR encephalitis patients have an abnormal EEG. The diffuse slowing is the most common presentation on the EEG. Extreme delta brush that is considered a pathognomic feature, mainly occurs in patients at the peak stage of the disease. EEG reflects the abnormal brain functions of patients and could assist with early clinical diagnosis [8].

NMDARs are predominantly found in forebrain and the limbic system and are known to play an important role in learning, memory, cognition and behavior [2, 9]. NMDA receptors are surface protein channels consisting of multiple subunits. Current data suggest that antibodies directed against the GluN1 subunit are responsible for this specific disease pathogenesis [10]. Anti-NMDAR antibodies are predominantly of the IgG1 subclass of IgG [11]. The antibody attachment to NMDA receptors, receptor crosslinking with subsequent internalization is the pathogenetic mechanism supported the most by current literature [2].

Typical course of the disease consists of several phases. Prodrome with flu-like symptoms is reported by up to 86% of patients, it is followed by initial psychiatric manifestations, later neurologic complications, recovery and late-phase sequelae [2]. Anti-NMDAR encephalitis patients often present first to a psychiatric clinic as they develop behavioral changes, memory deficits, hallucinations, paranoia and agitation—symptoms characteristic for the psychotic phase of the disease. These symptoms are followed by rapid decrease in consciousness and commonly epileptic seizures, at which point the patient is usually transferred to a neurologic ward or the ED (emergency department) [2, 12]. Patient prognosis is generally favorable with 75% of patients recovering to a near baseline neurological functioning [2]. A good prognosis is associated with early

diagnosis and treatment, milder symptoms and removal of tumor if present. Patients with non-paraneoplastic NMDAR encephalitis tend to recover slower and require longer hospitalization. Long-term outcome is associated with treatment responsiveness [2, 13]. We report a first ever confirmed adult case of autoimmune anti-NMDAR encephalitis in Latvia.

2. Case Description

A 25-year-old woman of Caucasian origin with no known history of psychiatric illness was admitted to RPNC (Riga Psychiatry and Narcology Center) due to emerging psychiatric disturbances. Ten days prior to hospitalization the patient was known to have experienced flu-like symptoms, later developed memory deficits, bizarre speech and started hallucinating. Otherwise her medical history appeared to be non-significant. She was treated with neuroleptics with no apparent amelioration of symptoms, in 3 days' time she became catatonic, developed fever and had progressive fluctuations in her state of consciousness. After having a generalized tonic-clonic seizure she did not regain consciousness and was transferred to RECUH (Riga East Clinical University Hospital).

On admission, her GCS (Glasgow Coma Scale) was 4, she was intubated and transported to the ICU (intensive care unit). Blood tests were performed showing leukocytosis, slightly elevated creatine kinase level, and increased levels of CRP (203.01 mg/L) and procalcitonin (0.335 ng/mL). A head CT was performed and showed no pathology. LP (lumbar puncture) was done, CSF (cerebrospinal fluid) analysis revealed lymphocytic pleocytosis of 103 cells with normal protein. Empiric therapy with Ceftriaxone and Acyclovir was started. She had repeated generalized tonic-clonic seizures, after receiving Diazepam she was started on continuous infusion of Sodium Valproate. With high suspicion of a NCSE (non-convulsive status epilepticus), she was started on a continuous infusion of Midazolam. An EEG

(electroencephalogram) was performed revealing diffuse slowing and functional changes with dominating delta activity and repetitive rhythmic generalized delta activity discharges of 3 Hz that last for 10 seconds—consistent with NCSE in repeated EEGs. Removal of midazolam was tried several times without success. Repeated myoclonic jerks of the extremities and periodic brachiofacial dystonia with orofacial dyskinezias were observed. Performed head MRI showed no pathology. Despite symptomatic and empiric therapy no improvement of patient's overall status was seen. Possible bacterial and fungal causes were excluded, no herpes group viruses were found positive in the CSF, tests for HIV, Lues, Lyme borreliosis and tuberculosis were negative. Considering patient history, laboratory data and clinical presentation with bizarre movements and a superrefractory status epilepticus, autoimmune encephalitis was suspected; in addition to glucocorticoids PLEX (plasma exchange) procedures were started. CT of the chest, abdomen and pelvis were performed and no malignancies were found. Repeated EEGs showed a baseline rhythm of delta waves and periodic beta flushing, burst-suppression-like changes could not be excluded.

After receipt of five consecutive PLEX procedures no significant improvement was observed. Patient's consciousness remained impaired, periodical opening of the eyes was seen but no contact could be made. Her overall status remained severe and a decision to start pulse therapy with Cyclophosphamide and high dose Methylprednisolone was made. After first administration of Cyclophosphamide the patient opened her eyes and started partially reacting to verbal commands. Facial dyskinezias, myoclonic jerks were still present. Therapy was continued and in two weeks' time (6 weeks after admission to RECUH) after Cyclophosphamide therapy initiation patient was conscious, able to obey commands. She was extubated and able to breathe spontaneously, however expressed negativism and remained mute. Seven weeks after

admission to RECUH the patient was discharged from the ICU and moved to a General Neurology department. A repeated lumbar puncture was done, CSF was tested for common autoimmune antibodies and was found positive for anti-NMDAR IgG. The patient was engaged in active rehabilitation and physiotherapy. Twelve weeks after admission to RECUH she was able to talk, sit and eat by herself, she could walk with assistance. She continued to express negativism, showed problems with cognition and memory up to the day of discharge. The patient was discharged 16 weeks after admission to RECUH with a modified Rankin Scale score of 3. She remained on immunosuppressive therapy with oral Cyclophosphamide for the next 3 months and continuous daily Prednisolone. No known side effects have occurred after patient's discharge. There are no data suggesting a tumor, however it has been recommended that the patient would undergo a screening for neoplastic disease once every 6 months at least for the next two years.

3. Discussion

Despite growing awareness and recognition of anti-NMDAR encephalitis, early diagnosis still remains a challenge and adequate therapy is frequently delayed for months. About 30% of patients who are later diagnosed with anti-NMDAR encephalitis are initially admitted to psychiatric centers. They often receive neuroleptics in high doses which leads to a relatively frequent misdiagnosis of malignant neuroleptic syndrome when presenting to the ED [12]. New-onset non-convulsive super refractory status epilepticus, autonomic instability and central hypoventilation are not rarely encountered in the course of autoimmune encephalitis—occurrence after a psychotic episode in a person with no history of psychiatric disease should raise suspicion of anti-NMDAR encephalitis [14-17]. Clinician's ability to diagnose and raise suspicion is of very high relevance. Our case once again highlights the need to raise awareness of such a disease entity in order to

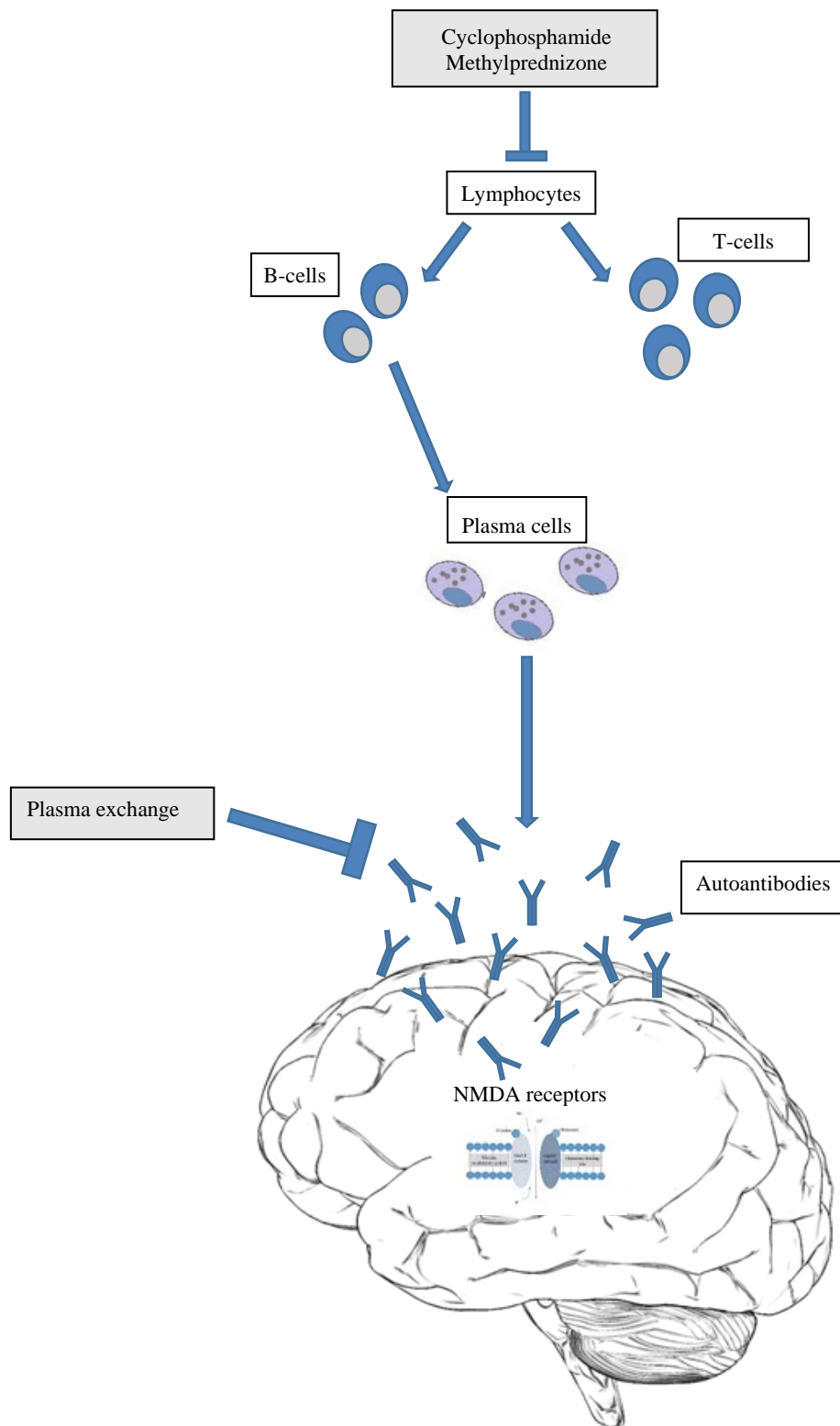


Fig. 1 The principles of action and targets of first-line and second-line therapy used in our patient. Corticosteroids suppress production of proinflammatory agents and differentiation of T-cells and in high doses induces production of anti-inflammatory proteins. Plasma exchange actively removes antibodies from the patient's serum. Frequently steroids and PLEX are used in combination in attempt to achieve a better outcome. Treatment with Cyclophosphamide affects both T and B cells.

achieve shorter therapy delay times as well as emphasizes the need to start 2nd line therapy as soon as possible due to considerable amount of patients who might respond only to that—as also seen in this case. Considering development of diagnostic criteria and approach recommendations for patients with suspected autoimmune encephalitis, early recognition rates are expected to grow [18, 19]. However, there are no internationally approved guidelines for the treatment of anti-NMDAR encephalitis making the next step of care in this disease yet another challenge. Therapy recommendations are based on experience and good clinical practice (Fig. 1). Corticosteroids, plasma exchange and IVIG alone or in combination are used in 1st line treatment [20]. There are known guidelines for glucocorticoid, IVIG therapy and plasma exchange procedures in autoimmune diseases, these principles are followed in treatment of autoimmune encephalitides, including anti-NMDAR encephalitis. Even so there are patients who do not respond to 1st line therapy demanding more aggressive approach. Second-line immunotherapy is required more often in patients with non-paraneoplastic anti-NMDAR encephalitis, as it is also demonstrated in our case report. Cyclophosphamide and B-cell targeted therapies and Rituximab are generally used as 2nd line treatment. Cyclophosphamide is considered a high-risk drug with various serious side effects, Rituximab could be a preferable agent. However, Cyclophosphamide is easily accessible and of lower cost than Rituximab [21]. It is not typically used in autoimmune neurological diseases and there are no accepted evidence based guidelines for dosing of Cyclophosphamide in anti-NMDAR encephalitis. Chosen therapy regimens are based on clinician's experience and case descriptions. In our case the patient received 3 cycles of intravenous Cyclophosphamide—2,000 mg monthly for 3 consecutive months. The total dose of each cycle was 30 mg/kg—higher than the usual dose used in rheumatological diseases, nevertheless lower than the preferred doses in oncology.

Anti-NMDAR encephalitis generally bears a good prognosis for the patient if diagnosed and treated early [13, 22]. When 1st line therapy failed, 2nd line therapy should be initiated. Our case raises the discussion of Cyclophosphamide usage *ex juvantibus* when specific antibody tests are not available. We believe the severity of the disease and risk-benefit ratio justifies taking action and starting treatment with Cyclophosphamide in refractory cases even if laboratory confirmation of anti-NMDAR antibodies is not available, provided that the criteria for probable anti-NMDAR encephalitis are fulfilled.

4. Conclusions

Newly onset psychosis in a patient with no prior history of psychiatric disease should raise suspicion, a CSF analysis might be recommended in such cases. Whenever autoimmune encephalitis is suspected, the patient's CSF should be tested for specific antibodies—as there are cases when NMDAR antibodies are found in the CSF but not in the serum. Clinical criteria proposed by Graus et al. in 2016 provide early diagnosis of anti-NMDAR encephalitis, it is highly advisable to follow the suggested approach. The criteria consist of clinical characteristics supported by instrumental and laboratory data, making it possible to make a definite diagnosis only after reasonable exclusion of other diseases—possible differential diagnoses should not be overlooked as treatment strategies might differ.

Although the awareness of autoimmune encephalitides is progressively growing, early diagnosis remains a challenge. Taking into account of the likely underestimation of the disease, exact incidence and prevalence of anti-NMDAR encephalitis in population remain unclear. Our case presents a rather classical manifestation of anti-NMDAR encephalitis. It highlights the importance of early recognition and treatment of suspected autoimmune encephalitis. Therapy should be initiated as soon as possible whenever autoimmune etiology of

encephalitis is suspected and 2nd line therapy should be used when 1st line therapy fails. Performing specific tests should not delay early treatment as prognosis gradually worsens with longer spontaneous duration of disease.

Acknowledgments

We would like to thank Dr. Oļegs Šuba (Toxicology and Sepsis clinic, RECUH) for providing professional and adequate intensive care in ICU and Dr. Normunds Sūna (Department of Neurology, RECUH) for recommendations with antiepileptic drug therapy as well as we would like to thank all other clinicians, physiotherapists and medical staff who participated in treatment and rehabilitation of our patient.

Funding

It is funded by Research Department of Rīga Stradiņš University.

Conflict of Interest Statement

None of the authors have potential conflicts of interest to be disclosed.

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