ACUTE PSYCHOSIS – ANTI-NMDA RECEPTOR ENCEPHALITIS PHASE

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INTRODUCTION

Anti N-methyl-D-aspartate (NMDA) receptor encephalitis is officially categorized in 2007, and has since then been recognized as the etiology of progressive encephalitis. It is caused by the autoimmune response primarily against NR1 NMDA receptor. It is associated mainly with tumors, especially ovarian teratomas and is therefore considered a paraneoplastic syndrome, although some patients do not have cancer (Lo et al. 2008). In case series published in 2008, 59% of patients had a tumor, most commonly ovarian teratoma (Dalmau et al. 2008). Based on reports of more large series of patients (n=577) with NMDAR encephalitis, 38% of patients had an underlying neoplasm, and 213 of these patients were women, representing 46% of all women (94% were ovarian teratomas) (Titulaer et al. 2013). The number of reported cases of anti-NMDA receptor encephalitis continues to grow exponentially, which means that this disorder is not rare and that there is growing awareness about the disease. Most cases of anti-NMDA receptor encephalitis occur in young women, 75% of the cases recover, while others become disabled or die (Dalmau et al. 2011).

Patients have a progressive syndrome in several phases. Prodromal phase usually consists of nonspecific symptoms such as headache, fever, nausea, vomiting and diarrhea (Iizuka et al. 2008). Within two weeks variable psychiatric symptoms begin to develop and may include anxiety, agitation, disorientation, manic behavior, psychotic episode and aphasia. A common feature is the loss of short-term memory. After that usually alternate agitation and catatonia (Consoli et al. 2011), abnormal movements, autonomic instability and seizures. The most common manifestations of autonomic nervous system are hypotension or hypertension, tachycardia or bradycardia, cardiac arrhythmias, hyperthermia, urinary incontinence and hypoventilation. These symptoms can be so severe as to require strong sedation and mechanical ventilation, and many patients require long-term treatment in intensive care units.

CASE HISTORY

A 34 year old woman was admitted for the first time to „Sveti Ivan“ Psychiatric Hospital in 2014, escorted by police after episode of aggressive and violent behavior at home. She was not being treated for mental disorder so far but five years before she had laparoscopic operation of the right ovarium due to endometriotic cyst. Earlier that day she received emergency psychiatric evaluation but she was not admitted to the hospital. In the week before the admission she was tense, anxious, hardly slept for five days and had auditory and visual hallucinations. Her behaviour was disorganized, she asked incoherent questions, feared that her partner would leave her, had mood swings, and she was saying that she relives her life from the beginning and that she was increasingly hearing sounds. On the day of admission she was forcing inmates out of the apartment, threatened them and pushed them, threatened to commit suicide with a sharp object, assaulted her partner and threatened him with a knife.

Two weeks prior to admission, the patient had a fever up to 39.1°C for several days, complained of headaches and tingling in the right temporal region. Routine urine examination revealed leukocyturia, urinary tract infection was diagnosed, amoxicillin/clavulanic acid was administered and fever receded.

The patient had a stressful job, alone in the night shifts, and she felt exhausted, afraid of going to work. Last six months before admission she was anxious, tense, and felt decreased in energy and fatigued.

Upon admission to the hospital she was paranoid, tense, anxious, described the phenomena of depersonalization and derealization, and affirmed experiencing hallucinations. She was afebrile and cardiopulmonary compensated without neurological deficits. She was also hypotensive, but with administered psychiatric drugs (ripseridon, fluvoxamine, diazepam, flurazepam) and the application of normal saline solution, blood pressure and clinical presentation became very variable. There were periods of improved mental condition, but...
initially requires the exclusion of other diseases. MRI is unremarkable in 50% of patients, while the remaining 50% of patients show non-specific changes which are usually mild and transient. EEG is altered in 90% of patients and usually shows non-specific changes (Dalmau et al. 2011). A study published in 2013 by Tiulaer et al. showed that MRI of the brain was abnormal in 33% of patients, and CSF studies were abnormal in 79% of patients. In study by Irani et al. (2010), high proportion (80%) of 44 NMDAR antibody-positive patients were without a detected tumor, while among them 29% were adult males and 29% children.

There are no established standard procedures in treatment of anti-NMDAR encephalitis, but as the antibody titer correlates with disease severity, main goal of therapy is to reduce or eliminate the level of anti-NMDAR antibodies (Dalmau et al. 2008). Positive and low positive anti-NMDA receptor antibody levels can be of clinical significance. Low positive NMDAR-Abs were identified in definite non-paraneoplastic anti-NMDAR encephalitis cases and in several cases rose to positive levels during the disease course. CSF anti-NMDA receptor antibodies are broadly related to serum levels in patients with tumors but in only 2/5 patients assigned as definitive. The selection of those patients in whom an immunotherapy intervention might be considered is irrespective of the antibody level and should be based on clinical features (Zandi et al. 2014). The prognosis depends on early recognition, prompt

**DISCUSSION**

A set of symptoms of anti-NMDAR encephalitis may seem confusing, but considering the fact that the majority of NMDA receptors are present in brain regions that are responsible for memory, personality, movement, cognition and control of the autonomic nervous system, it is not surprising that an increase in the antibody titres causes the loss of their functions (Dalmau et al. 2008, Day et al. 2011). During the first month of the disease most patients develop a similar spectrum of symptoms regardless of age. Based on reports of more large series of patients with NMDAR encephalitis, 65% of adults presented behavioral problems, while 50% of children below 12 years presented seizures or movement disorders (Titulaer et al. 2013). Pure psychiatric presentation of anti-NMDA receptor encephalitis could be associated with lower antibody titres (Barry et al. 2011). These episodes are rare, can occur as initial onset or relapse of anti-NMDA receptor encephalitis and their recognition is very important (Kayser et al. 2013). Misdiagnosis and referral to psychiatric services is common (Lawrence et al. 2014). Results from seven studies, comprising 1441 patients with psychosis (Pollak et al. 2014) showed that only 7.98% of patients were anti-NMDA receptor antibody positive. Diagnosis of anti-NMDA receptor encephalitis strongly relies on the clinical picture and the detection of anti-NMDA receptor antibodies in serum and cerebrospinal fluid. Clinical presentation occasionally her behavior was disorganized, she was confused, anxious and paranoid. Her sleep was partially regulated. On the eighth day of treatment she was aggressive towards medical staff. Occasionally she was somnolent or in a stupor. The prior therapy was discontinued and she was then treated with low doses of clozapine. Neurologist suspected that she had medical encephalopathy. Electroencephalogram (EEG) was normal. Sulpiride and haloperidol in low doses were added in therapy but the clinical presentation was still variable. Laboratory results from the beginning were within the reference range. Clozapine was then switched to olanzapine. Gradually she became negative and mute. The antipsychotics doses were reduced and discontinued, but patient was mainly deeply somnolent and mute. In third week of hospitalization she was febrile up to 38.5°C with pyuria and she was transferred to the University hospital for infectious diseases “Dr. Fran Mihaljević” in Zagreb for further medical evaluation and treatment, where she was mute and deepy somnolent with orofacial dyskinesia. The meningeal signs were negative. There were no focal neurologic deficits. Contrast enhanced brain CT was performed and the scan was normal. Cerebrospinal fluid (CSF) analysis revealed cell count 13 cells/mm³ (100% lymphocytes), protein level 0.47 g/l, and blood-brain-barrier analysis revealed intrathecal antibody synthesis. The CSF glucose level was normal. CSF bacteriology was sterile, and PCR for HSV1/2 was negative. Also, she was anti-HIV and TPHA negative. Soon after admission, the patient required intubation and mechanical ventilation due to the central hypoventilation and bradycardia. Abdominal ultrasound and gynaecological examination at the intensive care unit were normal. Due to the high clinical suspicion of autoimmune anti-NMDAR encephalitis, CSF and serum samples were analysed at the Prof. Josep Dalmau’s laboratory in Barcelona by immunohistochemistry and they were positive for anti-NMDAR antibodies. Brain magnetic resonance imaging (MRI) showed no abnormalities. The patient was treated with pulse doses of methylprednisolone, seven courses of plasmapheresis, corticosteroids and cyclophosphamide. During this treatment the patient was in critical condition, dependent on mechanical ventilation. There were no established standard procedures in treatment of anti-NMDAR encephalitis, but as the antibody titer correlates with disease severity, main goal of therapy is to reduce or eliminate the level of anti-NMDAR antibodies (Dalmau et al. 2008). Positive and low positive anti-NMDA receptor antibody levels can be of clinical significance. Low positive NMDAR-Abs were identified in definite non-paraneoplastic anti-NMDAR encephalitis cases and in several cases rose to positive levels during the disease course. CSF anti-NMDA receptor antibodies are broadly related to serum levels in patients with tumors but in only 2/5 patients assigned as definitive. The selection of those patients in whom an immunotherapy intervention might be considered is irrespective of the antibody level and should be based on clinical features (Zandi et al. 2014). The prognosis depends on early recognition, prompt
immunotherapy and complete removal of tumors in patients with paraneoplastic disease type (Dalmau et al. 2008, Lo et al. 2010). The best results were observed in patients who had tumor removed in combination with intense immunotherapy (Maggina et al. 2012). Recovery is usually slow and symptoms may relapse, especially in patients with no associated tumors and patients with undetected tumors (Dalmau et al. 2008).

There is a model that integrates anti-NMDA receptor encephalitis with a dysfunction of the GABA and glutamate. Antibody-mediated reduction of NMDA receptors may inactivate GABA neurons which serve to inhibit extracellular glutamate, and excessive secretion of glutamate can cause and exacerbate psychosis. A similar mechanism may be present in schizophrenia, so further studies may explain pathophysiological heterogeneity of schizophrenia (Keshavan & Kaneko 2013).

CONCLUSIONS

Anti N-methyl-D-aspartate receptor encephalitis remains under-recognized despite a growing body of literature, and prompt diagnosis of anti-NMDA encephalitis seems to be extremely difficult. It is particularly important to pay attention to the phases and symptoms of anti-NMDA receptor encephalitis because part of them mimic psychotic disorders and patients are often initially referred for psychiatric treatment, thereby delaying appropriate diagnosis and treatment of encephalitis.

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References


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