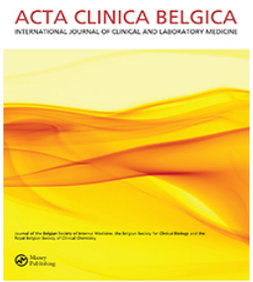

Acta Clinica Belgica
International Journal of Clinical and Laboratory Medicine

ISSN: 1784-3286 (Print) 2295-3337 (Online) Journal homepage: http://www.tandfonline.com/loi/yacb20

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To cite this article: Tine Hermans, Patrick Santens, Celine Matton, Kristine Oostra, Gunter Heylens, Sarah Herremans & Gilbert M. D. Lemmens (2017): Anti-NMDA receptor encephalitis: still unknown and underdiagnosed by physicians and especially by psychiatrists?, Acta Clinica Belgica, DOI: 10.1080/17843286.2017.1392077

To link to this article: http://dx.doi.org/10.1080/17843286.2017.1392077

ACTA CLINICA BELGICA, 2017
https://doi.org/10.1080/17843286.2017.1392077

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CASE REPORT

Anti-NMDA receptor encephalitis: still unknown and underdiagnosed by physicians and especially by psychiatrists?

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ABSTRACT

Anti-NMDA receptor encephalitis is an autoimmune disorder confirmed by the presence of antibodies against the NMDA-receptor in serum or CSF. This case report describes a young woman with anti-NMDA receptor encephalitis, who presented with prominent psychiatric symptoms. There was a crucial delay in diagnosis and necessary treatment due to the fact that the clinical presentation was diagnosed and treated as a first psychotic episode. Physicians and especially psychiatrists, should consider the possibility of an autoimmune encephalitis in their differential diagnosis in every new onset psychotic episode with rapid progression, the presence of pathognomonic orofacial dyskinesia, the lack of psychiatric history, and the non-responding to psychopharmacological treatment. Early diagnosis and treatment is essential for recovery and may improve the prognosis.

KEYWORDS

Anti-NMDA receptor encephalitis; acute psychosis; catatonia; orofacial dyskinesia

Introduction

Anti-N-methyl-D-aspartate-(NMDA) receptor encephalitis is an autoimmune disorder characterized by the presence of IgG autoantibodies against the GluN1 (also known as NR1) subunits of the NMDA-receptor [1]. The illness was first described in 2005, although the autoantibodies were detected in 2007 by Dalmau et al. [2,3]. The clinical presentation typically develops in different phases. More than 70% of the patients present with aspecific prodromal flue-like symptoms such as headache, fever, nausea, vomiting, diarrhea, upper respiratory symptoms, and fatigue. Psychiatric symptoms (e.g. agitation, delusions, auditory and visual hallucinations, disinhibited behavior, mood lability, depression, anxiety, disorganized thoughts, and behaviors), neurological problems (e.g. epileptic seizures, speech problems, and oro-lingual-facial dyskinesia), and cognitive impairment (e.g. confusion, short-term memory loss, and concentration difficulties) typically occur within 2 weeks following the prodromal phase. The disease then progresses over a period of weeks or months to a stage of decreased responsiveness (sometimes switching between increased agitation and a catatonic-like state) and autonomic instability (hyperthermia, tachycardia, hypertension, bradycardia, hypotension, and urinary incontinence) [4–6]. Exact prevalence rates are unknown, but more than 500 cases have until now been reported in the literature [4]. Age of onset varies from 8 months to 85 years, with a median age at onset of 21 years. When the age of onset is over 45 years (in only 5% of cases), the symptoms are less severe but outcome is mostly worse. The male/female ratio is 1/4 [6]. A clinical diagnosis of anti-NMDA receptor encephalitis can be confirmed by the presence of antibodies against the NMDA-receptor in serum or CSF. Other investigations have not proven to be contributory to the diagnosis. Brain magnetic resonance imaging is normal in 50–70% of the cases. Electroencephalograms are abnormal in 90% of the cases, showing slow and disorganized activity in the delta/theta range, but these findings are non-specific. In 60–80% of the cases, the CSF analysis is abnormal with a mildly increased protein concentration, presence of CSF-specific oligoclonal banding and a mild lymphocytic pleocytosis [4,5]. Once the diagnosis is confirmed, underlying neoplasia should be excluded. The odds for the presence of an associated neoplasm are dependent of age, sex, and ethnic background [1]. In approximately 50% of women older than 18 years an underlying tumor (most frequently an ovarian teratoma) is found, while in male patients the detection of a tumor is rare (only 5% >18 years). At younger ages associated tumors are less likely [5]. However, screening for an underlying neoplasm is mandatory in both sexes and at all ages in case of suspicion of a paraneoplastic encephalitis, as treatment of the underlying

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cause is essential [7]. A possible genetic risk is suggested by the fact that in Asian and Afro-American patients, the association of tumor presence with anti-NMDA receptor encephalitis is increased [5,6]. Besides the treatment of the underlying neoplasm when present [7], treatment options further include first-line immunotherapy (steroids, intravenous immunoglobulin and plasmapheresis; in combination or alone) and second-line immunotherapy (rituximab and/or cyclophosphamide). A recent observational cohort study suggests that more than 50% of the patients respond to first-line immunosuppression within four weeks. If no improvement is seen, it is recommended to use second-line immunotherapy. Regular screening for neoplasia over two years and pursued immunosuppression with mycophenolate mofetil or azathioprine for at least one year is advised in patients without a tumor, because relapse is more common in this population. A long-term reassessment of serum or CSF with absence of antibodies against the NMDA-receptor after treatment might be used as a marker for remission [4,5,7,8]. Predictors of a good outcome are early recognition, no admission to the intensive care unit, fast initiation of immunotherapy and neoplasm treatment if present. Full recovery or presence of mild sequelae is seen in approximately 75% of patients, the other 25% suffer from severe neurological deficits or die [4,7,8].

This case report describes a young woman with anti-NMDA receptor encephalitis, who presented with prominent psychiatric symptoms. This case report highlights the importance of early diagnosis and fast initiation of treatment (because it may improve the prognosis) and the need for physicians and especially psychiatrists to consider this disorder in their differential diagnosis in every new onset psychotic episode. The patient participated in the case report after giving her written informed consent and this study was approved by the ethical committee of the Ghent University Hospital.

Case presentation

A 25-year-old woman was admitted to a psychiatric ward of a general hospital because of paranoid and poisoning delusions, disorganized behavior and thoughts, logorrhea and (sexually) disinhibited behavior. Her medical and psychiatric history revealed no major abnormalities. The patient mentioned some problems at work one week prior to administration. There was no known family history of any psychiatric illness. Computerized tomography of the brain, urine toxicology, and routine blood showed no abnormalities. As she was diagnosed with a psychotic episode, she was treated consecutively with aripiprazole (10 mg/day) and a low dose of amisulpride. Because she developed extrapyramidal symptoms, the treatment was switched to olanzapine 10 mg/day. Despite the antipsychotic treatment, reality testing remained disturbed and psychotic symptoms worsened over the next weeks. Forty days after admission, she was transferred to a psychiatric hospital. At the time the patient showed catatonic symptoms such as mutism, perseveration, echolalia, frequent falls, and impulsivity leading to a frequent need for physical restraint to ensure the patient's safety. She was no longer able to eat or drink independently and she suffered from important weight loss. Because of frequent refusal to take her medication orally, she was administered olanzapine pamoate intramuscularly 300 mg two-weekly in combination with lorazepam 1.5 mg/day. Twelve days later, she was transferred to the emergency department of a university clinic due to a fall causing a wound on her chin that required treatment. The clinical and mental examination showed a pale, thin, and extremely anxious woman with psychomotor retardation. There was poor responsiveness, impression of perseverative verbal behavior and echolalia. There was eye contact when spoken to. She was not oriented in time and place. Muscle tone was rigid in all four limbs and neck without presence of involuntary movements. Neurological examination did not disclose any focal signs. She had a Glasgow Coma Scale of 11/15, vital parameters were within normal range. Her blood showed diffuse electrolyte disorders (most likely due to the anorexia) and a minor inflammation (probably because of diffuse hematomas after repeatedly falling). The patient was diagnosed with catatonia and hospitalized on the emergency psychiatric unit for further observation. She was treated with lorazepam 10 mg/day and the antipsychotic medication was stopped. Further, a fracture of the right humerus was diagnosed (on X-ray) requiring urgent surgery. Because the patient's condition worsened due to increasing confusion and agitation, fever, tachycardia and autonomic instability, she was transferred to the intensive care unit for 6 days and afterward to the neurology ward where she stayed for 2 months. When admitted to the neurology ward, she clinically presented with catatonia (echolalia, mutism, perseveration, stupor, catalepsy, gegenhalten, and posturing) and orofacial dyskinesia (mainly tongue movements). Lumbar puncture and brain magnetic resonance imaging (MRI) revealed no major abnormalities. Electroencephalogram (EEG) was mildly retarded and revealed intermittent bifrontal bursts of monomorphic delta waves. No evidence of epileptiform discharges was found. As anti-NMDA receptor encephalitis was suspected, serum and CSF samples were sent for evaluation of antibodies. In the meantime, a short treatment (3 days) with high doses of intravenous methylprednisolone was tried, without significant effect. Because of a lack of clinical improvement of the catatonia, electroconvulsive therapy (ECT) was started. After the first ECT session, the patient suffered from three epileptic seizures and levetiracetam 1000 mg/day was started (and later increased till 1500 mg/day because of another epileptic episode with brachio-crural clonus). Serologic results confirmed the diagnosis of anti-NMDA receptor encephalitis the

same day of the first ECT session and ECT treatment was stopped. After treatment with plasmapheresis and intravenous methylprednisolone 500 mg/day the patient started to improve, although major cognitive defects and catatonic symptoms remained present. Pelvic computerized tomography and magnetic resonance imaging, gynecological examination (including pelvic ultrasound) and a PET-CT of the whole body did not demonstrate presence of neoplasia. When plasmapheresis was temporarily stopped for two weeks (because of antibiotic treatment for an urosepsis), orofacial dyskinesia, confusion, and psychotic symptoms rapidly deteriorated again. Plasmapheresis two times a week was restarted in combination with methylprednisolone (64 mg on plasmapheresis days) and mycophenolic acid 500 mg/day was added to the treatment. Over the next few weeks the patient's condition improved and the catatonic symptoms disappeared. Because cognitive problems (more specifically problems with attention, memory and executive functions) and a right-sided hemiparesis persisted, more intensive cognitive and physical rehabilitation was started. The plasmapheresis and steroid treatments were stopped after 18 and 15 weeks, respectively. Mycophenolic acid was increased to 2 × 500 mg. Psychiatric symptoms as well as cognitive and neurological problems gradually disappeared during the following 5,5 months (4 months inpatient and 1,5 months outpatient treatment) at the rehabilitation center. Mycophenolic acid was finally stopped after a cutaneous herpes infection. Finally, also levetiracetam was stopped. Ten months after the start of the illness, the patient was almost fully recovered and the level of psychosocial functioning has returned to the premorbid state with a part-time job, a new relationship, and independent living.

Discussion

We report the case of a young woman with anti-NMDA receptor encephalitis who remained undiagnosed and untreated for several weeks. The time until confirmation of the diagnosis was precisely 74 days. There are several explanations for this crucial delay in diagnosis and necessary immunotherapeutic treatment. First, the patient presented primarily with psychiatric symptoms (delusions, disorganized behavior and thoughts, logorrhea and (sexual) disinhibited behavior), which were regarded to be provoked by problems at work. No neurological complications (e.g. epileptic seizures) were present at onset. Secondly, routine investigations (brain imaging, lumbar puncture, blood and urine sample, EEG,…) revealed no major abnormalities. Consequently, the clinical presentation was diagnosed and treated as a first psychotic episode within a primary psychiatric disorder. Finally, the delay between clinical suspicion and serologic confirmation of the diagnosis (almost 3 weeks) contributed to the extended interval.

However, the clinical presentation and its progression should have led sooner to the consideration of the diagnosis of an anti-NMDA receptor encephalitis. Firstly, the initial presentation with primarily psychiatric symptoms, even without major neurological complications or cognitive impairment, does not exclude the diagnosis of an anti-NMDA receptor encephalitis. A new onset psychosis is described in the literature as the most common initial diagnosis of anti-NMDA receptor encephalitis [4]. Secondly, there was a rapid progression over two to three weeks from a psychotic to a catatonic state, with only little to no response to psychopharmacological treatment (e.g. antipsychotics and benzodiazepines). Thirdly, the normal premorbid functioning and lack of any prodromal symptoms typical for the onset of schizophrenia, the absence of important personal and familial psychiatric history, and the absence of a significant effect of antipsychotics made the diagnosis of an underlying psychiatric disorder such as schizophrenia or bipolar disorder rather unlikely [7]. Negative urine drug screening and the absence of history of substance abuse excluded further a drug-induced psychotic state. Fourthly, the evolution to a stage of autonomic instability should have been explained by an underlying psycho-organic cause. Finally, the presence of orofacial dyskinesia (e.g. tongue movements) may have pointed to the diagnosis of an anti-NMDA receptor encephalitis. These were in our case seen as extrapyramidal side effects of the antipsychotic medication.

Because the initial diagnosis of a psychotic episode, treatment with antipsychotics was started. However, in case of an anti-NMDA receptor encephalitis, the use of antipsychotics may complicate the diagnosis. The development of movement disorders (e.g. muscular rigidity and akathisia), decreased responsiveness, and autonomic instability may be mistaken for a malignant neuroleptic syndrome [4,6]. This was the case in our patient. Because of the rapid progression to a catatonic state, antipsychotics were stopped and lorazepam 10 mg/day was started. Benzodiazepines (more specifically lorazepam) are the first-choice treatment for catatonia, regardless of the underlying condition [4,9]. Because of a lack of clinical improvement of the catatonia with lorazepam, electroconvulsive therapy (ECT) was started. After confirmation of the diagnosis of anti-NMDA receptor encephalitis (by the presence of antibodies against the NMDA-receptor in CSF), first-line immunosuppression with plasmapheresis and intravenous methylprednisolone was started, with good clinical response [4,5,8].

Because early treatment may positively influence the prognosis, the question arises whether one should start immediately with screening for the presence of an underlying neoplasia (in women specifically an ovarian teratoma) and offering adequate treatment (immunotherapy and tumor removal if present) as soon as an anti-NMDA receptor encephalitis is clinically suspected, even before final confirmation of the presence of NMDAR antibodies.

Finally, this case demonstrates that, despite the presence of several negative prognostic factors (e.g. long lasting catatonic state, late treatment, admission to the intensive care unit, and the absence of an underlying tumor) prognosis can still be good. Our patient showed only amnesia for the entire acute phase of the illness, which is commonly observed [1,6]. She showed good recovery with no major psychiatric, neurological, or cognitive abnormalities. Intensive follow-up and periodic screening for neoplasia (in particularly for an ovarian teratoma) is recommended and currently ongoing in our patient since relapse is more common in patients without a tumor present. Almost two years after the onset of the episode, our patient is still doing well. She is living alone, has a relationship and started a part time job.

Conclusions

Patients presenting with new onset psychotic symptoms without any psychiatric history and no risk factors associated with or without the onset of neurological or systemic complaints should be fully screened to exclude underlying causes before a diagnosis of a psychiatric disorder can be made. Autoimmune encephalitis and especially anti-NMDA receptor encephalitis typically presents with atypical psychiatric symptoms and should be taken into account as a potential differential diagnosis. Red flag symptoms are rapidly progressive psychotic symptoms, the lack of any psychiatric history or prodromal features, the presence of neurological or systemic complaints and the non-responding to psychopharmacological treatment. Following clinical suspicion, testing for antibodies against the NMDA-receptor and early screening for an underlying neoplasm, including a pelvic ultrasound in women, should be performed since a prompt diagnosis and fast initiation of treatment might be essential for recovery.

Consent

For the publication of this case report, we obtained a written informed consent from the patient and her family.

Disclosure statement

No potential conflict of interest was reported by the authors.

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