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CASE REPORT

Encephalitis with anti-NMDA receptor antibodies: paraneoplastic or non-paraneoplastic?

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Summary

We report the case of an encephalitis patient with anti-N-methyl-D-aspartate receptor (NMDAR) antibody positivity. Anti-NMDAR encephalitis is a relatively rare autoimmune disease. In our patient, the diagnosis of anti-NMDAR encephalitis was established as late as several months after the first manifestations of the condition. Further development demonstrated that the patient probably suffered from a paraneoplastic form of the disease, although the presence of an underlying tumour was not detected by the available imaging methods at the time of diagnosis. The case is a rarity since the disease usually affects females, and only 5% of adult male patients have a paraneoplastic aetiology.

INTRODUCTION

Encephalitis with anti-NMDA receptor antibody positivity is a recently identified form of encephalitis with an autoimmune pathogenesis and a characteristic clinical picture dominated by psychiatric symptoms. It was first described by Dalmau *et al.* (2007) in a group of 12 female patients with ovarian teratoma in whom the disease occurred as a paraneoplastic syndrome. Anti-NMDAR encephalitis is associated with a tumour in approximately half of the cases. In female patients, the underlying tumour is usually ovarian teratoma, in males testicular teratoma, and rarely another tumour type (e.g. small-cell lung cancer) is detected. Although the disease affects women more frequently (in 80 %) than men, particularly young women (median age 23), all age groups may be affected. Newly diagnosed cases suggest that the disease is one of the most common immune-related encephalitides (Pollak *et al.*, 2016). It is likely that a substantial proportion of cases have been misdiagnosed with a different, usually psychiatric condition. Anti-NMDAR encephalitis is potentially lethal, yet prognosis may be favourable in case of properly targeted therapy.

The disorder is part of a broader group of autoimmune limbic encephalitides. These immune-mediated conditions are divided into syndromes with antibodies to intracellular antigens and syndromes with antibodies to membrane and synaptic antigens.

Several days before disease development, the clinical picture shows non-specific, flu-like symptoms (subfebrile temperature or fever, headache, nausea, upper respiratory tract symptoms, general discomfort). These are followed by psychiatric symptoms - anxiety, agitation, disorientation,

behavioural impairments, insomnia, auditory and visual hallucinations, delusions. Most cases progress towards neurological symptoms such as seizures, movement disorders, autonomic instability, hypoventilation up to consciousness disorders and catatonic-like states (Kayser a Dalmau, 2016).

Diagnosis of anti-NMDAR encephalitis is based on the detection of specific autoantibodies of the IgG class. Tests are carried out on serum as well as cerebrospinal fluid (CSF) using the immunofluorescence method. In half of the patients, the abnormality is imaged by magnetic resonance (MR) of the brain, usually showing slight and transient cortical hyperintensities on fluid-attenuated inversion recovery (FLAIR) sequences in the medial temporal lobe region or enhancement of the meninges following gadolinium administration. Abnormal electroencephalogram (EEG) is found in most patients. The recordings are often non-specific, with generalized or localized slow activity, but epileptic EEG activity may also be recorded. Every patient with suspected anti-NMDAR encephalitis needs to have complete cancer screening done involving a lung X-ray, abdominal/pelvic ultrasound and a whole-body PET/CT scan. Patients should continue to be followed even when the findings are negative because the current diagnostic methods may not be sensitive enough to reveal the tumour. Early and aggressive immunosuppressive treatment together with tumour removal (if there is a tumour) results in a favourable outcome in a large proportion of the patients (Titulaer *et al.*, 2013; Oldham, 2017).

CASE REPORT

A 59-year-old male patient was admitted to the psychiatric ward in August 2013 due to the development of psychosis in the last two weeks. He had been trained as an electrician and worked as a manual worker. He was a smoker and abused alcohol. He underwent unilateral orchiectomy 12 years ago due to seminoma. He was not under further oncological follow-up and did not suffer from any other serious illnesses. He had not received psychiatric treatment before. Two months prior to psychosis onset, he had been hospitalised in an infectious diseases department for febrile temperatures and mild cough persisting for 10 days. The assessments carried out did not reveal the cause of his complaints. Brain CT did not show any pathology. EEG recordings showed slow wave frequency over both posterior quadrants and were limited by frequent artifacts with no epileptiform discharges. After the febrile temperatures faded, the patient was discharged home with a diagnosis of "aseptic neuroinfection of unclear aetiology". No changes in his mental condition were observed while he was hospitalised in the infectious department.

The patient's wife described significant mental changes in the last two weeks. She reported that he was confused, was seeing cameras at home, thought that he was being followed by secret police and that they were going to kill him, he did not recognize family members, was helpless, not oriented in everyday situations, he was hearing a foreign male voice and claimed to be 9 years old. Upon examination, he was disoriented to time, place and partly person. Psychomotor tempo was slower. His responses were mostly out of the question category. He made a helpless impression. His emotivity was exaggerated and mood was dully euphoric. The patient's thinking was loosened or even incoherent, with a paranoid persecutory delusion. Auditory verbal and probably also visual hallucinations were evident. Cognitive performance was decreased (Mini Mental State Examination – MMSE 21 points). Speech disorders appeared (phatic disorder, echolalia). He was sometimes aggressive to other patients. Severe disorientation persisted and his thoughts were completely incoherent. The patient was treated with levomepromazine 50 mg daily and olanzapine 20 mg daily. While on this medication, the patient gradually became calmer and more cooperative. Neuropsychological assessment was performed. Cognitive function deficit was apparent with dominant impairment of executive functions, manifesting primarily as reduced inhibition of stimuli (internal – vulgarity, digressive thinking; external – loose associations to the environment), worsened fluency and thinking flexibility, and impaired ability to understand and carry out an instruction. The other functions (memory, orientation) seemed to have been impaired secondarily to the impairment of executive functions.

When the patient's condition improved, magnetic resonance imaging of the brain could be performed.

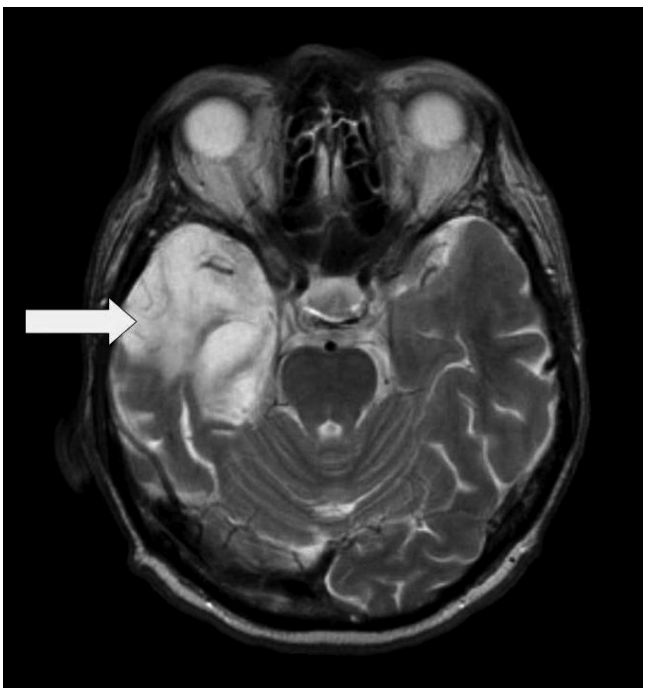

Fig. 1. Brain MRI, T2 sequence – significant local atrophy of the right temporal lobe

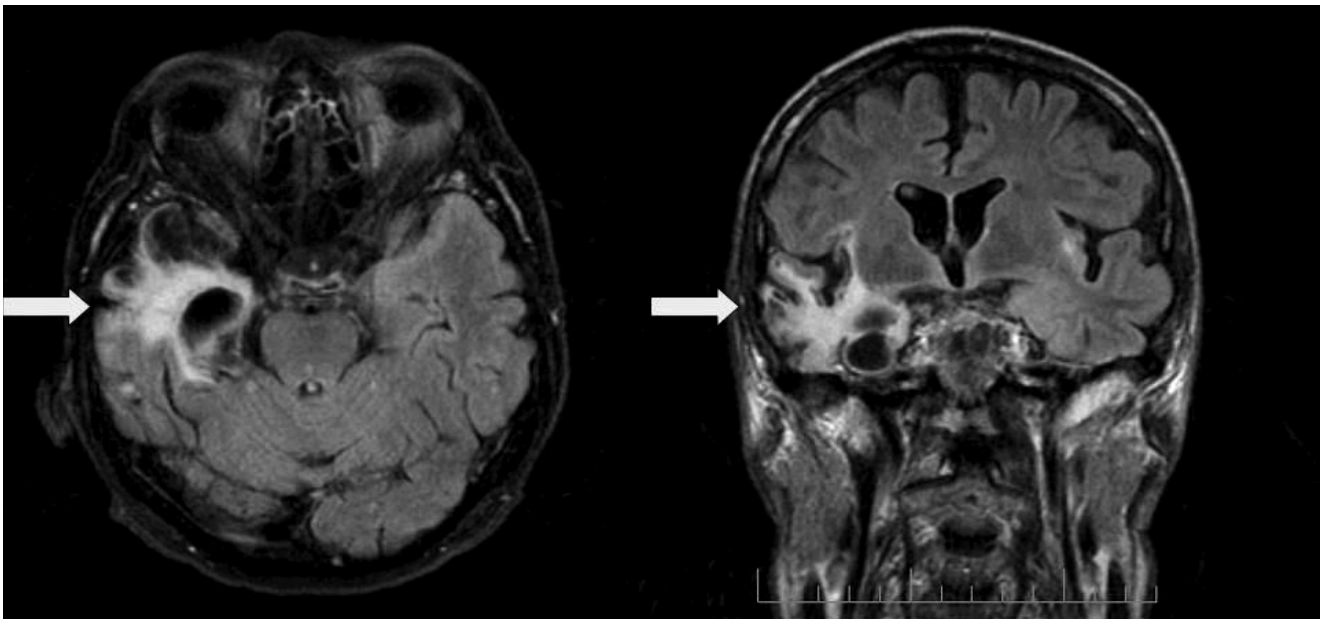

Fig. 2. Brain MRI, FLAIR sequence – significant local atrophy of the right temporal lobe with cystic degeneration

The imaging examination showed significant atrophic changes in the right temporal lobe, most pronounced in the area of the hippocampus with surrounding gliosis and cystic degeneration. Imaging also showed a minor atrophy in the region of the sylvian fissure on the left-hand side (Fig. 1 and 2).

Lumbar puncture and other laboratory tests were performed. CSF analysis showed decreased lymphocyte counts and the presence of oligoclonal antibody synthesis. At the same time, serum tested positive for NMDAR antibodies, other onconeural antibodies being negative. After seven weeks of hospitalization in the psychiatric ward, the patient was transferred to a neurological ward. Oncological screening was performed with no evidence of recurrence or a new cancer (oncomarkers, whole-body PET/CT). EEG was abnormal due to slowing, most pronounced over the right temporoparietal region, but there was a clear improvement in the organization of the recorded EEG activity when compared to previous recording.

Additional CSF examination showed a continued decrease in lymphocyte count. CSF testing for NMDAR antibodies was also carried out showing NMDAR antibody positivity as well as a higher antibody titer when compared to serum testing. The serum anti-NMDAR antibody titer gradually decreased. The patient's overall clinical status improved significantly, and therefore immunotherapy was not initiated. Follow-up brain MRI two more months later did not show any new changes. The dose of antipsychotic medication was gradually decreased. Cognitive skills gradually improved; only mild memory impairments persisted.

The patient returned home. Initially, he needed to be cared for by his former wife, but started to engage in daily activities. Six months later, he was able to function independently. Neuropsychological assessment showed that only a mild cognitive impairment persisted. The patient attended regular outpatient psychiatric check-ups and was not taking any psychotropic drugs. He also received oncological follow-up.

In January 2015, the patient was diagnosed with generalized pancreatic carcinoma and palliative chemotherapy was initiated. He died in May 2015, two years after the first manifestation of anti-NMDAR encephalitis.

DISCUSSION AND CONCLUSION

The case we have described is unusual in several regards. The diagnosis of autoimmune encephalitis was established only after a number of months from the first symptoms, following psychosis onset. Then there was the question of a possible relation between the illness and the seminoma that the patient had suffered from, that is, paraneoplastic aetiology. However, no evidence of seminoma recurrence or other cancer was found. Therefore, the diagnosis of non-paraneoplastic anti-NMDAR encephalitis was established. After 18 months, however, a generalized pancreatic tumour was detected in our patient. Further development thus showed that a paraneoplastic form of the disease was probably concerned, and diagnosis needed to be re-evaluated. If no tumour is detected, oncological follow-up of the patient is still recommended for at least two years (Titulaer *et al.*, 2013). Cases have been described in published literature where the tumour was detected as late as several years after encephalitis manifested itself (Iziuka *et al.*, 2010). Our case demonstrates that these recommendations need to be followed in practice even if the patient's condition returns to normal and he or she has no major

complaints. Literature suggests that only about 20% of the described cases of anti-NMDAR encephalitis concerned male patients and that a tumour was detected only in 5 % of male patients older than 18 years (Dalmau *et al.*, 2011).

The question remains when psychiatric symptoms first appeared in our patient. None were mentioned in the medical records while he was hospitalized in the infectious department. The first EEG at the time when the patient's complaints began contained a significant amount of artifacts due to the patient's uncooperativeness, and it is therefore likely that some mental changes did already occur when this EEG was recorded. During the two months between the febrile state of unclear aetiology and the onset of the patient's psychosis, his wife observed only slower psychomotor tempo and reduced performance.

Despite the findings of pronounced atrophy and gliosis of the right temporal lobe, the clinical status improved significantly over a few months, demonstrating considerable adaptability of the central nervous system.

In each patient, NMDAR antibody testing needs to be done both on serum and on CSF. Serum antibody positivity has also been described in other, mainly psychiatric conditions (narcolepsy with psychotic symptoms, schizophrenia). Antibodies in CSF, however, are specific for anti-NMDAR encephalitis (Dalmau *et al.*, 2011). When the investigation is performed after a longer period of time or the patient has already received immunotherapy, antibodies may be detectable only in CSF. Similar results were found in our patient. While follow-up serum testing showed only low antibody levels, their positivity in CSF was convincing as late as several months after the disease onset.

There have been reports of cases of slow and spontaneous disappearance of antibodies (both in serum and CSF) and the resulting clinical improvement without previously administered immunotherapy as well as without existing tumour removal (Ezeoke *et al.*, 2013; Iziuka *et al.*, 2008). Such recovery lasts for several months or years.

Published literature has reported mostly slight and transient changes on MR brain images, if any changes are detected at all (Kayser a Dalmau, 2016). In our patient, prominent involvement of the right temporal lobe was imaged: despite our ignorance of the patient's condition prior to disease onset, we regard this as a sequel of anti-NMDAR encephalitis. However, it remains unclear whether the extent of the changes resulted from the relatively late diagnosis, or whether the illness would have had a similarly destructive course even with early therapy.

Anti-NMDAR encephalitis should be included in the differential diagnosis in encephalitides of unclear aetiology, in patients with newly diagnosed psychosis without previous psychiatric history and displaying other associated symptoms such as dyskinesia, seizures and autonomic instability. Cases manifesting only through psychiatric symptoms and memory impairments may mimic a psychotic condition (Pollak *et al.*, 2016). Correct diagnosis is then not established in practice and the patients are treated with antipsychotic drugs at a standard psychiatric care unit. Some cases diagnosed as "first-episode psychosis" are in fact manifestations of anti-NMDAR encephalitis. Treatment, however, is fundamentally different. Instead of antipsychotics, early initiation of immunosuppressive therapy may lead to positive treatment outcomes (Lennox *et al.*, 2012).

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REFERENCES

1 Dalmau J, Tuzun E, Wu HY, Masjuan J, Rossi JE, Voloschin A et al (2007). Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. **61**: 25–36.
2 Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R (2011). Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. **10**: 63–74.
3 Ezeoke A, Mellor A, Buckley P, Miller B (2013). A systematic, quantitative review of blood autoantibodies in schizophrenia. Schizophr Res. **150**: 245–251.
4 Iizuka T, Yoshii S, Kan S, Hamada J, Dalmau J, Sakai F et al (2010). Reversible brain atrophy in anti-NMDA receptor encephalitis: a long-term observational study. J Neurol. **257**: 1686–1691.
5 Iizuka T, Sakai F, Ide T, Monzen T, Yoshii S, Iigaya M et al (2008). Anti-NMDA receptor encephalitis in Japan: long-term outcome without tumor removal. Neurology. **70**: 504–511.
6 Kayser MS, Dalmau J (2016). Anti-NMDA receptor encephalitis, autoimmunity, and psychosis. Schizophr Res. **176**: 36-40.
7 Lennox BR, Coles AJ, Vincent A (2012). Antibody-mediated encephalitis: a treatable cause of schizophrenia. Br J Psychiatry. **200**: 92-94.
8 Oldham M (2017). Autoimmune Encephalopathy for Psychiatrists: When to Suspect Autoimmunity and What to Do Next. Psychosomatics. **58**: 228-244.
9 Pollak TA, Beck K, Irani SR, Howes OD, David AS, McGuire PK (2016). Autoantibodies to central nervous system neuronal surface antigens: psychiatric symptoms and psychopharmacological implications. Psychopharmacology (Berl). **233**: 1605-1621.
10 Titulaer MJ, McCracken L, Gabilondo I, Armagué T, Glaser C, Iizuka T, et al (2013). Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. **12**: 157-165.