children participating in a longitudinal study at Time 1 (6 to 8 years old), Time 2 (18 months after Time 1), and Time 3 (36 months after Time 1), as well as for a separate adolescent sample (14 to 17 years). The M100 response slowly develops over time (with earlier maturation in the right than left), with no left or right M100 response observed at Time 1. At Time 3, left and right M100 responses are evident but not yet with the full development shown in the adolescent sample.

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Persistently positive anti-NMDA receptor antibodies in chronic psychotic disorder: foe or innocent bystander?

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Isolated psychiatric manifestations of Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis have been recognized[1] and NMDAR antibodies have been described in first psychotic episodes (FEP).[2] Their clinical significance in chronic psychosis is a subject of debate and uncertainty about immunotherapy usefulness remains.[3] We present a patient with chronic late-onset psychosis, persistently positive NMDAR antibodies (Immunoglobulin G against NMDAR GluN1 subunit, detected using a cell-based immunofluorescence assay) and no clear response to immunotherapy.

A 64-year-old man with a 10-year chronic psychotic disorder and probable diagnosis of schizophrenia, with multiple psychotic relapses and under treatment with quetiapine 800 mg, was admitted to our psychiatry ward with persecutory delusions and auditory and visual hallucinations. He presented negative symptoms and cognitive deterioration and there were no abnormal movements, catatonia, seizures, autonomic instability or respiratory distress. No triggers were reported for relapse.

The patient had a probable neuroleptic malignant syndrome (NMS) 7 years ago, while being treated with haloperidol.

One year before the current admission, due to a psychotic relapse and a positive syphilis test, a lumbar puncture was performed to rule out neurosyphilis.

Cerebrospinal fluid (CSF) testing revealed normal cell count, increased proteins (0.91 g/dL, normal range: 0.1–0.3), positive NMDAR antibodies and one oligoclonal band. CSF VDRL test and antibodies against non-NMDAR cell surface antigens and intracellular antigens were negative. Serum NMDAR antibodies were positive. Brain Magnetic Resonance Imaging showed non-specific white matter hyperintensities probably related to small vessel disease. Electroencephalogram (EEG) revealed intermittent slow activity with overlapping abrupt waves, without "extreme delta brush" pattern. Blood count, creatinine, urea, liver enzymes, thyroid-stimulating hormone and thyroxine levels were normal. HIV and hepatitis viruses were negative. Neoplasms were excluded with chest-abdomen-pelvis computed tomography and testicular and thyroid ultrasound. Alpha-fetoprotein and prostate-specific antigen levels were normal. Cognitive assessment revealed significant impairment of attention, executive functions, visuospatial abilities, working memory and language. There was no history of previous infections that could be related to NMDAR antibodies appearance. The patient was treated with quetiapine 800 mg.

During current psychotic relapse, CSF testing was repeated, revealing increased proteins (1.01 g/dL), positive NMDAR antibodies and no oligoclonal bands. Serum NMDAR antibodies remained positive. NMDAR encephalitis was considered a possible diagnosis (positive antibodies and warning signs: probable NMS and EEG/CSF abnormalities), despite the atypical presentation and the long course of psychosis. The patient was started on intravenous methylprednisolone. After 2 days he became confused and psychotic symptoms worsened, thus steroids were stopped. He was then offered five sessions of plasmapheresis, with no clear clinical benefit. Due to psychosis chronicity, cognitive impairment and no clear response to first-line immunotherapy, it was decided not to proceed to second-line treatments. Quetiapine was switched to olanzapine 15 mg. At hospital discharge, the patient displayed improved positive symptoms, with residual delusions. Cognitive deterioration and negative symptoms persisted.

In more than 66% of patients, NMDAR encephalitis presents with acute psychiatric symptoms and usually progresses rapidly to include neurological features.[4,5] While the majority of patients develop this multistage progression, isolated psychiatric symptoms were described.[1] Warning signs suggesting an autoimmune etiology include CSF and EEG abnormalities or history of NMS, as reported in this case. Other signs include decreased levels of consciousness or abnormal movements, which were not present.[6,7]

An increased prevalence of NMDAR antibodies in FPE has been described, ranging from 3% to 6.5%.[2,8] However, literature regarding the prevalence of those antibodies in chronic psychosis is heterogeneous.[3] In a case series of 43 patients with chronic refractory psychosis, three were positive for NMDAR antibodies in serum.[9] Data regarding treatment options in patients with isolated psychosis and positive NMDAR antibodies is scarce. In a case series including patients with acute psychosis, positive NMDAR antibodies and no clear neurological involvement, nine were treated with immunotherapy and six achieved symptomatic remission.[10] Two patients with long course refractory psychosis did not achieve sustained response.

We report a challenging case, as the pathological relevance of persistent serum and CSF NMDAR antibodies (detected at two time points, one year apart) in this case chronic psychosis is uncertain and clear-cut treatment recommendations have not been determined. In our case, the patient had an unclear response to immunotherapy. Doubts remain whether this represents a treatment failure or if NMDAR antibodies were an incidental finding. The authors speculate that lack of response to immunotherapy was due to delay in treatment. NMDAR antibodies may have played a role in the pathogenesis of psychosis and cognitive impairment, being a foe, not an innocent bystander.

Symptom description and case discussion based on NMDAR encephalitis and autoimmune psychosis criteria are available in Supporting Information (S1-S2).

Signed consent was obtained from the patient authorizing publication.

Disclosure statement

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Supporting Information S1 Patient's clinical symptoms description

Supporting Information S2 Case discussion based on current NMDAR encephalitis and autoimmune psychosis criteria

Supporting Information S3 Author contributions

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