CASE REPORT

Autoimmune limbic encephalitis presenting as relapsing psychosis

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SUMMARY

A 34-year-old woman with a history of relapsing psychosis presented with a 15-month history of impassivity and social withdrawal associated with cognitive impairment. The subsequent recurrence of psychomotor agitation, auditory hallucinations and delusional thinking resulted in an emergency admission under psychiatric services. Initial investigations, including MRI of the brain and cerebrospinal fluid studies were unremarkable and she was treated for a primary psychiatric disorder. The diagnosis of autoimmune limbic encephalitis was established after further investigations revealed the presence of antibodies to the NR1 subunit of the *N*-Methyl-D-aspartate receptor (NMDAR). Immunotherapy resulted in rapid resolution of psychosis and marked improvement in cognitive and social function. This case underlines the importance of considering anti-NMDAR encephalitis within the differential diagnosis of psychosis associated with cognitive impairment even in those with an apparent previous psychiatric history and response to antipsychotics.

BACKGROUND

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis typically presents with a severe multistage encephalopathy with stereotypic progression. Up to 70% of such cases present with non-specific constitutional and flu-like symptoms, developing psychosis and memory impairment within a fortnight.[1 2] This is followed by a phase of language disintegration, ranging from reduced verbal fluency to echolalia and mutism, and catatonia.[1] The subsequent development of central hypoventilation, dysautonomia, seizures and refractory dyskinesia often results in intensive therapy unit (ITU) admission[1] especially if there are delays in establishing the diagnosis or introducing immunotherapy.[3 4]

Anti-NMDAR encephalitis has emerged as the commonest cause of hitherto unclassifiable encephalitis accounting for 3% of such cases in one series[5] and 4% of all ITU encephalitis admissions in another.[6] While the incidence and prevalence of this condition is unclear, the number of cases appearing in the literature since its first description has led some investigators to suggest that it is likely to be an underestimated disorder.[1 7]

While the majority of cases described to date follow the clinical progression described above, there is increasing awareness that atypical forms[8 9] of anti-NMDAR encephalitis exist which present with prominent psychiatric symptoms.[9–11] The presentation in this instance as an acute psychosis mimicking schizophrenia and the excellent response to immunotherapy highlights the critical importance of raising awareness of this disorder and its expanding phenotype, particularly within clinicians working in acute psychiatric services.

CASE PRESENTATION

In 2007, a 29-year-old right-handed African woman presented to psychiatric services with third-person and command auditory hallucinations accompanied by delusional and paranoid ideation. She was treated with neuroleptic agents and gradually returned to baseline social and intellectual functioning over a 2 month period. She was entirely asymptomatic between 2007 and December 2010, during which time she was weaned off antipsychotic therapy, completed a higher diploma and gained employment as a health-care assistant.

In December 2010 symptoms recurred, on this occasion preceded by dysphoria and emotional detachment. The positive symptoms of psychosis improved spontaneously over 2 months but she remained in an impassive and abulic state, requiring supervision with all aspects of daily life and unable to return to work.

She was treated with antidepressants but developed worsening cognitive impairment. In July 2011, she had difficulty recognising family members and friends. At outpatient review in September 2011, the presence of impaired speech fluency, inattention and progressive memory impairment prompted a referral to a tertiary cognitive disorders clinic. There were no significant features of paranoia, hallucinosis or delusional thinking during this period of community-based care. Brain MRI performed at this time was unremarkable.

In 2012, evaluation in the tertiary clinic revealed flat affect and temporal disorientation. Bedside psychometric assessment, limited by inattention, revealed severe impairment of declarative memory (recent and remote autobiographical events, recent newsworthy items), prosopagnosia and visual associative agnosia. Category-specific semantic memory impairment was also present. The Mini-Mental State Examination (MMSE)[12] score was 20/30.

While awaiting further investigations a recurrence of psychomotor agitation, auditory hallucinations and delusional thinking resulted in an emergency admission under psychiatric services. She was subsequently transferred to the regional neurosciences unit for diagnostic workup. Upon transfer, she displayed fluctuating alertness and lucidity with episodes of psychomotor agitation during which her speech was noted to be incoherent and

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perseverative. Severe inattention and agitation precluded formal neuropsychometric assessment.

INVESTIGATIONS

Basic blood tests (including B_{12}, thyroid function testing and syphilis serology) were normal, an autoimmune screen for rheumatological conditions was negative and the urine sediment was non-reactive. The cerebrospinal fluid (CSF) was acellular with normal biochemical constituents. An MRI brain scan (with diffusion-weighted sequences) was unremarkable. The patient refused EEG, believing it would 'erase her mind'. She was transferred back to the psychiatric unit for further management of an evolving psychotic syndrome, with the addition of risperidone and aripiprazole improving agitation but she developed an apathetic, withdrawn state with on-going auditory hallucinations. Antithyroid peroxidase, antivoltage gated potassium channel and antiglutamate decarboxylase antibody assays were subsequently found to be negative.[13 14] Other laboratory results received at this point revealed unmatched oligoclonal bands in the CSF and high titres of serum IgG antibodies to the NR1/NR2b subunit of the NMDAR (score 4, normal range 0–0.5; semiquantitative assay performed by the Department of Clinical and Experimental Neuroimmunology, University of Oxford, UK).[7] This established the diagnosis of anti-NMDAR encephalitis. CSF NMDAR antibody assays were not routinely performed at this time.

DIFFERENTIAL DIAGNOSIS

The initial differential diagnosis encompassed those disorders resulting in an atypical presentation of primary psychosis associated with cognitive impairment or a rapidly progressive dementia syndrome presenting with prodromal psychosis. The diagnoses thus considered included limbic encephalitis, schizophrenia-related cognitive impairment and rapidly progressive neurodegenerative dementias.[15] Prion disease, specifically variant Creutzfeldt-Jakob disease (CJD), was relevant given the rate of cognitive decline, the duration of the current symptom complex and the presence of prominent neuropsychiatric symptoms.[16] However, while cognitive decline is recognised as a core deficit of schizophrenia,[17 18] the degree of cognitive impairment, particularly of episodic memory and higher visual processing was considered more indicative of organic pathology.[19–21]

TREATMENT

The patient was initially treated with concurrent intravenous immunoglobulin (2 g/kg total dose) and methylprednisolone (5 g in total), administered over 5 days. Subsequently she was treated with plasma exchange followed by oral prednisolone (0.75 mg/kg) in combination with mycophenylate mofetil (500 mg twice daily).

OUTCOME AND FOLLOW-UP

In light of the well-described association between anti-NMDA encephalitis and ovarian teratoma,[1 2] the patient was screened for an underlying neoplasm, including whole body CT scanning and transvaginal ultrasonography, with negative test results.

By day 7 of her initial treatment, she was able to recognise family but inattention, auditory hallucinations and visual agnosia persisted. An EEG revealed diffuse slow wave activity but no frank epileptiform activity. In view of this limited response to therapy, plasma exchange was started on day 14. By day 21, there was complete resolution of hallucinations. At discharge on day 28, she was self-caring with return of insight and resolution of paranoid ideation. A pre-discharge EEG was completely normal. On discharge, the modified Rankin Score (MRS)[22] was two compared to a nadir score of four prior to initiating treatment. At 3 month review, the MRS was 1 with an MMSE of 30.

From a functional perspective, she regained insight and was fully independent in all aspects of childcare, home and personal care. Repeat cognitive assessment revealed mild frontal–subcortical dysfunction manifest as impaired abstract reasoning and psychomotor speed but without any features of idiosyncratic, circumlocutory or fragmented speech. There was residual semantic paraphasia but improvement in overall speech fluency, confrontational naming, information encoding and delayed recall of verbal information. She remains seropositive for IgG NR1/NR2b antibodies to the NMDAR. There has been no recurrence of positive psychiatric symptoms.

DISCUSSION

Anti-NMDAR antibodies have been detected in 6.5% of patients presenting with first-episode psychosis, some of whom meet diagnostic criteria for schizophrenia.[10] Importantly, not all such patients require immunotherapy and both spontaneous clinical resolution[7 10 23] and a response to modified electroconvulsive therapy[9 24 25] have been described in this clinical context. Nonetheless, the successful reversal of symptoms in those individuals with a primarily psychiatric presentation[7 9 26] has highlighted the importance of maintaining vigilance for this disorder as an organic cause of psychosis. Similarly, the initial co-occurrence of acute psychosis accompanied by episodic memory impairment, seizures or a movement disorder is suggestive of antibody-mediated encephalitis particularly if initial infective and neoplasm screens are negative.[5 14 27] While the application of NMDAR antibody testing to chronic schizophrenia has been less rewarding,[28] our case further highlights the need to consider this condition not only in those with initial psychosis[4 10 26] but also in the setting of relapsing positive psychotic symptoms allied to progressive cognitive decline.[25]

Relapses in anti-NMDAR encephalitis are well described in the context of multistaged disease in a cohort that has usually already been treated previously with either immunotherapy and/or tumour removal.[2 29] In such cases, disease relapses are usually milder and dominated by neuropsychiatric symptoms.[2 4] In this case, the relapsing and spontaneously remitting nature of disease with varying intervals between increasingly florid psychoses increased the risk of misdiagnosis. With regard to the profile of initial cognitive impairment, the deficits of attention, working memory, episodic memory and executive function are in keeping with those described following an episode of typical (multistaged) anti-NMDAR encephalitis.[30] The fact that a similar psychometric profile, albeit with a lesser degree of episodic memory impairment, is associated with schizophrenia[19 21 31] underlines further the importance of diagnostic awareness of this condition. By contrast with the other cognitive deficits described above, to our knowledge this is the one of only two descriptions of prosopagnosia occurring in the context of anti-NMDAR encephalitis.[32] The co-occurrence of prominent semantic memory impairment and prosopagnosia are reminiscent of symptoms seen in patients with temporal variant fronto-temporal dementia with focal degeneration primarily involving the left [33] and right anterior temporal lobe[34 35] respectively. This corresponds to regions of atrophy previously reported in anti-NMDAR encephalitis[2 7] but interestingly is outside the brain regions known to be particularly dense in NR1/NR2 NMDAR.[24]

It has previously been suggested that predominantly psychiatric forms of anti-NMDAR encephalitis are uncommon and usually reflect a failure to recognise other disease

manifestations.[2] However, it is difficult to know what proportion of cases may present in this way since such patients are not at present routinely tested for anti-NMDAR antibodies. Our experience with this case echoes this sentiment but does highlight certain 'red-flags' that need to be considered when cognitive impairment alone accompanies a schizophrenia-like illness.

The literature to date would suggest that the majority of younger patients with anti-NMDAR encephalitis have primarily autoimmune rather than paraneoplastic disease.[4 7 4 36–38] This cohort often present with an abrupt or acute onset of psychosis or behavioural change accompanied by memory impairment, mutism or insomnia which may serve as early clues of the underlying diagnosis.[2 36 39 40] These initial symptoms are consistent with the known distribution and hypofunction of NR1/NR2 NMDAR in the basal forebrain, limbic system and hypothalamus.[24] In anti-NMDAR encephalitis the causative IgG autoantibodies produce reversible internalisation and hypofunction of glycine/glutamate NMDA receptors by binding to an extracellular epitope of the NR1 (glycine) subunit.[1] This reversibility may account for the excellent response usually seen with early immunotherapy and/or tumour removal and more than two-thirds of patients may expect complete or near-complete recovery in this setting.[4] However, relapses occur in up to 25% of patients that present with the typical, multistage form of anti-NMDAR encephalitis usually in individuals with unrecognised paraneoplastic disease, primarily autoimmune disease or those not initially treated with immunotherapy.[4 41] It is currently unknown what proportion of patients with spontaneous remission eventually relapses. It is, however, worth noting that relapses have been described as early as 3 months to as late as 9 years after the initial illness.[41]

Current guidance suggests the application of first-line immunotherapy in instances where initial clinical, MRI or CSF evaluation supports the diagnosis of autoimmune encephalitis.[27 42] This initially involves a combination of high-dose intravenous methylprednisolone (1 mg/day for 5 days) and intravenous immunoglobulin (2 g/kg over 3 days). Plasma exchange may be considered as an empirical next step if this approach initially fails or produces an incomplete therapeutic response. Should these measures fail to provide acute control and only if an autoimmune diagnosis is felt to be unambiguous (e.g. seropositive, brain biopsy), more aggressive second-line therapies are considered, which may include rituximab and cyclophosphamide. Given the known higher relapse rate and likelihood of poor outcomes in patients with autoimmune anti-NMDAR encephalitis, some authorities advocate early and aggressive immunotherapy with a low threshold for switching to second-line agents if there is no clinical response.[4 27] However, currently there is no evidence to suggest that any particular first-line agent is of benefit over another and importantly no clear guidance on when to initiate long-term immunosuppression although mycophenylate mofetil, azathioprine[4 27] and methotrexate [7] have been cited as reasonable choices in patients requiring a prolonged course of steroids or maintenance immunosuppression. Importantly, while both CSF and serum antibody titres are known to fall with effective immunotherapy, the present literature does not suggest this to be of particular relevance in patients with improving clinical parameters.[4 7]

In summary, our case, along with another recently described in the literature[25] is characterised by an initial presentation with a brief acute psychotic episode followed by a prolonged asymptomatic phase, with the diagnosis of anti-NMDAR encephalitis established after an abrupt recurrence of positive psychiatric symptoms. The dramatic improvement post-immunotherapy highlights the importance of considering this disorder in the differential diagnosis of acute psychosis, even in context of a history of neuroleptic-responsive psychosis.

Learning points

- Anti-*N*-Methyl-D-aspartate receptor (NMDAR) encephalitis typically present with psychiatric symptoms, most often psychosis preceding development of severe multistage encephalitis. However, there is increasing awareness of atypical variants of this disease in which the initial psychotic symptoms dominate and may be misdiagnosed as schizophrenia.
- The cognitive deficits that evolve in this disorder are more severe than those typically associated with schizophrenia.
- Anti-NMDAR encephalitis responds excellently to early immunotherapy and more than two-thirds of patients can expect near complete recovery.
- Some patients with anti-NMDAR encephalitis may remit spontaneously and caution is required in assessing patients with prior psychosis who present with other features suggestive of systemic upset or limbic dysfunction.
- The true prevalence of anti-NMDAR encephalitis may be under-recognised.

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