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ANTI-NMDA ENCEPHALITIS IN THE ACUTE SETTING

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SUMMARY

Background: *Encephalitis associated with antibodies targeted against the N-methyl-D-aspartate (NMDA) receptor is increasingly recognised as a major cause of an acute presentation of organic psychosis. Misdiagnosis and subsequent inappropriate referral to psychiatric services is common and avoidable. This review focuses on addressing this issue in the acute setting.*

Methods: *The authors present a review of existing literature relating to the pathophysiology and presentation of anti-NMDA receptor encephalitis, prior to proposing a management pathway avoiding delays to treatment incurred through misdiagnosis or inappropriate referral.*

Conclusions: *Acute care physicians should have a low threshold for suspecting anti-NMDA receptor encephalitis in any patient presenting with acute psychosis in the context of non-specific coryzal and constitutional symptoms in whom infective causes have been excluded. The presence of pleocytosis and reduced protein in routine CSF analysis should further raise suspicion, and samples should be sent for immunohistochemical testing. Availability and efficiency of this testing is currently suboptimal.*

Key words: *anti-NMDA receptor encephalitis - organic acute psychosis*

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INTRODUCTION

Auto-antibodies targeted against the NMDA receptor have become increasingly publicised as a cause for a severe, treatable subtype of encephalitis. Despite this, the majority of patients with the condition experience a delay in referral to the appropriate services, with misdiagnosis and inappropriate admission to a psychiatric unit commonplace (Braakman 2010, Dalmau 2008, Irani 2010, Parthasarathi 2006, Tsutsui 2012, Zandi 2011).

NICE guidelines for acute psychosis in a secondary care setting recommend a multidisciplinary assessment of acute presentations of psychosis including a medical assessment to identify physical illness including organic brain disorders (Breese 2012, National Institute for Health and Care Excellence 2014, Schimmel 2009). With recent studies showing anti-NMDA receptor antibodies to rival viruses as a leading cause of encephalitis (Gable 2012), an understanding of the condition amongst acute care physicians is vital. This article presents the current understanding of the disease and details the investigations and management that should be prompted by careful history taking and examination in the emergency department.

PATHOPHYSIOLOGY

A new subtype of treatable encephalitis was first identified in 2005 by Vitaliani et al., who reported cases of paraneoplastic encephalitis associated with ovarian teratoma. The subsequent development of sensitive and reproducible assays revealed a further non-neoplastic population of patients with clinically indistinguishable symptoms to those with ovarian teratoma (Dalmau 2008, Irani 2010).

The postulated role of autoantibodies was confirmed by the isolation of IgG1 antibodies reacting with the extracellular N-terminal domain of the NR1 subunit of the NMDA receptor in patient serum and CSF (Dalmau 2007, 2008, Vitaliani 2005).

Brain biopsies of patients have revealed perivascular lymphocyte cuffing and microglial activation, while CSF tests have shown a high prevalence of lymphocytic pleocytosis, oligoclonal bands and intrathecal synthesis of NR1 antibodies in these patients. The overall result is a selective and, crucially, a reversible decrease in NMDA-receptor clusters post-synaptically as a result of the patients' antibodies (Dalmau 2008).

PRESENTATION IN THE ACUTE SETTING

The typical presentation initially involves non-specific coryzal and constitutional symptoms, before invariably progressing to a psychotic stage, including bizarre behaviour, confusion, visual or auditory hallucinations and catatonic movement disorder (Dalmau 2008, Tsutsui 2012, Wandinger 2011). Left untreated, the patient can deteriorate with a reduced level of consciousness, development of seizures, central hypoventilation, involuntary movements and autonomic instability (Tsutsui

2012). It is usually only after the deterioration of patients to this degree that an organic brain disease is considered (Dalmau 2007).

Though these are the most common clinical sequelae, there is a broad range of documented phenotypes, with presentations including tonic-clonic seizures, pure ataxia and isolated Broca's aphasia (Aguiar de Sousa 2014, Deiva 2014, Titulaer 2013). Furthermore, the dominant presenting feature will vary with patient age. Seizures and behavioural symptoms occur with equal frequency in children (<12years), with behavioural symptoms becoming increasingly common with age (Titulaer 2013).

The past medical history of the patient will often be unremarkable, with the exception of the paraneoplastic subtype who may be known to oncology services. Peak incidence is in the late teenage years in the non-neoplastic subtype, and early in the third decade in the neoplastic subtype (Titulaer 2013).

INVESTIGATIONS

Retrospective analysis has shown MRI scanning to be of low sensitivity for detecting anti-NMDA receptor encephalitis, with only half of patients demonstrating increased FLAIR or T2 signal in brain regions (Dalmau 2008). Similarly, electroencephalography has been shown to have little value in diagnosis. Serum and CSF analysis therefore form the basis of diagnostic testing. Comparison of routine CSF analysis in those with viral and anti-NMDAR encephalitis has shown decreased levels of protein and pleocytosis in those with a diagnosis of the latter (Gable 2012). Definitive diagnosis requires immunohistochemical testing of patient CSF and serum to reveal NMDAR auto-antibodies, which may not be readily available (Dalmau 2007). This method of diagnosis has been shown to have sensitivity of 100% when analysing CSF and 85% when analysing serum (Titulaer 2013).

MANAGEMENT CHALLENGES

Immunotherapy is the primary treatment for anti-NMDA receptor encephalitis that can include corticosteroids, intravenous immunoglobulin, plasmapheresis, rituximab, or cyclophosphamide (Gable 2012). There is also limited evidence suggesting a possible role for modified electric convulsion treatment (mECT) (Mann 2012, Tsutsui 2012).

The largest cohort study of patients with anti-NMDA receptor encephalitis reported a 7% mortality, 18% with severe neurological deficits and a further 28% of patients with mild neurological deficits (Dalmau 2008). This compares to up to 100% survival for patients with Herpes Simplex Viral Encephalopathy presenting with organic psychosis and promptly treated with acyclovir (Chaudhuri 2002).

There is limited but emerging evidence early treatment improves outcomes in anti-NMDA receptor encephalitis (Breese 2010, Schimmel 2009, Yau 2013). With respect to its paraneoplastic aetiology, earlier immunotherapy treatment for the tumour has been shown to result in statistically significant improved outcome and reduced neurological relapses (Dalmau 2008). However, the prompt management of this condition continues to be inhibited in two ways. Firstly, immunohistochemistry testing has been shown to take in excess of two weeks for results to be confirmed (Chapman 2011). In an effort to avoid neurological sequelae as a result of delayed treatment, some case reports have evidenced improved outcomes with empirical treatment with a presentation of acute psychosis with an unknown cause (Byrne 2014).

Secondly, there is a substantial evidence base of case reports identifying misdiagnosis or inappropriate referral to psychiatric services in the management of anti-NMDA receptor encephalitis in the acute setting (De Nayer 2009, Ito 2010, Khadem 2009, Maramattom 2010, Nasky 2008, Parratt 2009, Piehl 2010, Sonn 2010, Suzuki 2009, Tan 2010). These two factors together may be contributing to the high mortality and risk of neurological sequelae for a reversible pathological process.

CONCLUSION

Case reports and retrospective cohort studies have identified numerous inappropriate referrals of patients with anti-NMDA receptor encephalitis to psychiatric services in the acute setting. Given the complex nature of definitive testing for the disease, it is reasonable to expect that a combination of a clinical picture in keeping with anti-NMDA receptor encephalitis and a routine CSF analysis showing low protein and pleocytosis should prompt a low threshold for treatment as anti-NMDA receptor encephalitis, assuming infective causes of encephalitis have been ruled out. This early consideration of NMDA receptor encephalitis in the acute presentation would reduce unnecessary investigations and procedures resulting in a more prompt and cost-effective treatment (Gable 2012).

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