Case report

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Anti-N-methyl-D-aspartate encephalitis – a case study of symptomatic progression

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Abstract

Objective: To present the diagnosis course and sequelae of a case of anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, drawing attention to early psychiatric symptoms.
Method: The literature on anti-NMDA encephalitis is reviewed and possible psychopathological mechanisms discussed.
Result: New onset psychoses, presenting with the combination of hallucinations, dyskinesias and seizures and progressing to catatonia should be referred to neurology for consideration of anti-NMDA receptor encephalitis.
Conclusion: Early diagnosis is important for a favourable prognosis.

Keywords: N-methyl-D-aspartate receptor, catatonia, dyskinesia, dopamine, mania

Introduction

The present study examines in detail the progression of psychopathological symptoms in a 15-year-old girl, patient C of Malaysian Chinese descent, who presented at Accident and Emergency at a major children's hospital with an agitated delirium, first thought to be either psychosis or viral encephalitis, but diagnosed soon after admission to be anti-N-methyl-D-aspartate (NMDA) encephalitis.

Findings in relation to anti-NMDA receptor encephalitis have drawn attention to the importance of both early recognition and treatment of the condition, as well as a better understanding of the psychopathology of neuronal receptor mediated conditions. Dalmau et al.[1] reported a case series of NMDA encephalitis and commented on the need for further studies to clarify the role of prodromal events in triggering the immune response, molecular events involved, as well as the best type and duration of immunotherapy. According to the authors, all 100 patients in their series presented with psychiatric or memory problems, 76 had seizures, 88 unresponsiveness, 86 dyskinesias, 69 autonomic instability and 66 hypoventilation. Fifty eight patients had tumours – most commonly ovarian teratomas, all of which contained nervous tissue.

Presentation

Patient C presented to Accident and Emergency at a major hospital with a 4-day history of insomnia, worsening agitation with significant restlessness at night and withdrawal during the day. Her parents observed her to have been speaking quickly, jumping from one topic to another and making inappropriate and grandiose comments such as being a rock star, with flight of ideas

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and some pressure of speech. Prior to her presentation, there was a 2-week history of deterioration in sleep pattern after returning from a 6-day family trip to Singapore. She also reported vivid visual, tactile and auditory hallucinations closer to the time of presentation.

There had been contact in Singapore with a relative suffering gastroenteritis but no infective or systemic symptoms in the patient. She did not have a history of illicit substance use or mental health problems. Examination on the day of admission revealed an alert but agitated girl, who was apyrexial but tachycardic and hypertensive, possibly consistent with her level of agitation. ENT, chest and abdominal exam were unremarkable. Neurological examination revealed mildly slurred speech, tremor of her upper limbs at rest with generalised 4+/5 weakness, increased tone and slightly brisk reflexes. Baseline bloods including full blood count, urea, electrolytes and creatinine, liver function tests, cell membrane proteins, C-reactive protein, venous blood gas, lactate were all unremarkable. Creatinine kinase was slightly elevated at 540 U/l and urine screening for illicit substances was negative.

On the second day of admission, the patient remained hypertensive and tachycardic and spiked an isolated temperature reading of 38°C. Agitation deteriorated with worsening speech production and a wide based gait. Electrocardiogram was within normal limits, electroencephalography (EEG) showed mild generalized slowing but no epileptiform activity. Magnetic resonance imaging brain showed minor non-specific findings. Lumbar puncture showed pleocytosis (18 white cells, 0 red cells, 0 polymorphs, 16 mononuclears, two degenerated cells, with no organisms or culture growth). Glucose and protein levels were within normal limits. The sample was sent away for further testing, excluding infective causes of encephalitis including adenovirus, Epstein-Barr virus, enterovirus, human immuno-deficiency virus and varicella zoster virus. Repeat creatinine kinase showed a rise in the level to 2536 U/l and was considered to be possible neuroleptic malignant syndrome in a neuroleptic naïve girl after receiving high doses of antipsychotics to treat agitation and behavioural disturbance. Screening for auto-antibodies serum and cerebro-spinal fluid were sent on day 2 to screen for anti-NMDA receptor antibodies.

Over the next 3 days, the patients' presentation worsened, particularly at night, with little sleep. She was observed by parents and hospital staff to be experiencing perceptual disturbance and showed odd, purposeless movements including hand wringing, repetitive folding of blankets, lability of mood and pressured speech using mostly unintelligible words, worsening agitation requiring restraint from two to three nursing staff. Given the deterioration in presentation and suspicions of autoimmune (anti-NMDA) encephalitis, the patient was also commenced on intravenous methylprednisolone 1 g for 5 days, followed by prednisone 50 mg daily thereafter and intravenous immunoglobulin (IVIg) 1 g/kg for 2 days, by day 3 while results were pending. Repeat creatinine kinase had further risen to 4525 U/l.

Over the following week, the patient further deteriorated, was in a state of persistent confusion with very little sleep, fluctuating consciousness and had associated urinary incontinence requiring catheterization. She developed a number of automatisms such as chewing, confirmed on EEG to be non-epileptic and progressively developed dyskinesias of her limbs and later oro-facial movements of chewing, biting and bruxism, autonomic instability with spikes in temperature readings, fluctuations in blood pressure and heart rate, which required treatment with clonidine. By day 7, the diagnosis of anti-NMDA receptor encephalitis was reported and confirmed on day 14.

Clinical presentation necessitated a further two IVIg doses at 1 g/kg by day 11. Despite this, the patient deteriorated further with poor swallow and oral intake requiring naso-gastric tube feeding, persistent low grade pyrexia, worsening speech and communication, muttering of unintelligible words and there was development of generalised tonic-clonic seizures, requiring the commencement of an anticonvulsant, sodium valproate. The clinical presentation was complicated by development of aspiration pneumonia and E.coli urinary tract infection.

Between the second and third week of hospital admission, the patient was unresponsive and demonstrated features of catatonia including mutism, cogwheeling, rigidity, posturing and negativism. She displayed rhythmic smacking and pursing movements of the lips, with positive glabellar tap and the Immunology team were consulted for advice regarding commencement of rituximab, second line immunotherapy as first line immunotherapy had failed. This was later administered on day 17 and again on day 27. Between 6 to 8 weeks after the patient's admission, some improvements in clinical condition were observed. Consciousness, speech and communication improved, vital signs began to stabilize and she was able to briefly recall some of her hallucinatory experiences.

Patient C underwent initial neuropsychological assessment over four sessions during weeks 10, 11 and 16 of her admission. The initial assessment results revealed deficits in areas of new learning of verbal and visual material, auditory memory and working memory, speed of processing, word finding and executive functioning in the context of average intellectual abilities. She demonstrated executive deficits in areas of reasoning, flexibility, emotional regulation and initiation. There was evidence of only subtle gains in her executive functioning between weeks 10–11 and 16. Patient C was reviewed 6 months later, approximately 10 months post-onset of the encephalitis. She impressed as confident and initiated conversation. Formal test results showed significant gains in her logical reasoning, word finding, speed of processing and visual memory skills, all of which now fell within normal limits. The main residual weaknesses identified were in the domains of auditory attention span, free recall of language-based material from memory and executive functioning in the domains of mental flexibility and working memory.

Possible mechanisms

The NMDA receptor is a glutamate receptor, which plays a crucial role in synaptic transmission, plasticity and memory.[2] The receptors are ligand-gated cation channels and heteromers of NR1 subunits, binding glycine and NR2 subunits that bind glutamate.[3] There are several proposed mechanisms through which antibodies targeting NMDA receptors exert their effects leading to the clinical characteristics described in many case reports. NMDA receptor hypofunction is the main proposed underlying mechanism. Dalmau and colleagues determined that the extracellular NR1 subunit was the main epitope targeted by antibodies and by using enzyme linked immunosorbent assay to measure antibody titres showed that patients' antibodies decreased numbers of cell surface NMDA receptors in post-synaptic dendrites.[1]

Teratoma with neural tissue

Anti-NMDA receptor encephalitis is often classed as a paraneoplastic syndrome. It is the cross-reactivity of antibodies produced by the body's immune system in response to the presence of ectopic brain tissue, usually a teratoma, with the extracellular epitope on the NR1subunit of the NMDA receptor that is thought to be involved in the pathogenesis of the disease.[4]

Dalmau et al. first identified NMDA receptor antibodies in 12 women with ovarian teratomas, who presented with neuropsychiatric symptoms and autonomic dysfunction.[5] A later review of 400 patients showed that age, gender and ethnicity affects the presence of a tumour.[6] In women older than 18 years with anti-NMDA receptor encephalitis, 55% had an ovarian teratoma compared to only 15% of women younger than 14 years and African Americans had a higher frequency of ovarian teratomas.[6]

Given these complex effects, the sequence of observed phenomena in any one case of anti-NMDA encephalitis may be interpreted in terms of an initial non-specific widespread delirium accompanied by oro-facial and limb dyskinesias with subsequent cortical excitability and seizures or catatonia, followed by autonomically mediated effects on ventilation, although the order of these effects may vary. Thus, identification via antibody detection at the stage of early delirium/psychosis, accompanied by unusual motor effects, is very important in order to achieve rapid control of the immune response and prevention of the life-threatening implications of later effects on ventilation, as well as possible recurrence rates.

In our patient, a more typical presentation with multisystem involvement led to early diagnosis and institution of appropriate first and second line immunotherapy. According to Dalmau et al.,[6] the constellation of symptoms in anti-NMDA encephalitis can suggest alternative diagnoses at different stages. While adults are often diagnosed with a new onset psychosis, and treated with antipsychotic medication, this can result in rigidity, autonomic instability and increased muscle enzymes, mistaken for neuroleptic malignant syndrome. Other patients have been diagnosed with viral encephalitis or encephalitis lethargica, but in the presence of dyskinesias were later shown to have anti-NMDA antibodies. The authors concluded that any individual, especially under 50 years of age, especially a child or a teenager, who develops a rapid change of behaviour or psychosis, abnormal postures or movements, seizures and variable signs of autonomic instability, hypoventilation or both should be suspected of anti-NMDA encephalitis. A recent meta-analysis of the association between NMDA receptor antibodies and schizophrenia, schizoaffective disorder, bipolar disorder and major depressive disorder found that individuals with schizophrenia or schizoaffective, bipolar or major depressive disorders are collectively about three times more likely to have elevated NMDA receptor antibody titres compared with healthy controls.[7]

Discussion

The present case raises the question of differential diagnosis of agitated delirium in a previously well teenager and illustrates the importance of psychiatric/neurological collaboration. In the above case, the history of grandiosity coupled with flight of ideas and hallucinations could have suggested an early schizoaffective or hypomanic disorder, although the presence of visual hallucinations coupled with confusion and delirium at presentation was more suggestive of encephalitis, while the development of dyskinesias and catatonia suggested dopaminergic/glutamatergic involvement, resembling the effects of phencyclidine and NMDA blockade.

The progression of symptoms from a possible affective psychosis to seizures, dyskinesia and catatonia presented considerable management challenges, not the least of which related to two to three nursing requirements for physical safety. The present case indicated that immunological investigations should be carried out at an early stage, particularly as anti-NMDA receptor encephalitis is treatable and early treatment is likely to be important for prevention of progression to autonomic and respiratory failure. It illustrates the importance of psychiatric/neurological collaboration at early stages and raises the question of when immunological investigations should be carried out, particularly as early treatment may be important for prevention of residual neurological impairment.

Conclusion

New onset psychoses, presenting with the combination of sudden behaviour change, hallucinations, seizures and dyskinesias and catatonia should be referred for consideration of anti-NMDA receptor encephalitis.

Disclosure

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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