CASE REPORT

Early consideration of anti-NMDAR encephalitis in unexplained encephalopathy

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With the identification of anti-NMDAR (N-methyl-D-aspartate receptor) antibody, the spectrum of anti-NMDAR encephalitis has been expanding. The condition is also increasingly recognised in children, though younger patients are less likely to have tumours, while behavioural and speech problems, seizures, and abnormal movements are common early presenting features. Here we present yet another case with subtle, non-specific clinical symptoms that responded promptly to intravenous immunoglobulin. We believe this illustrates the importance of considering this uncommon differential diagnosis in the management of unexplained neurological conditions.

Introduction

Since the first report of anti-NMDAR (N-methyl-D-aspartate receptor) encephalitis by Dalmau et al in 2007,[1] its spectrum of clinical features has been expanding, from typical psychiatric symptoms and epileptic seizures to movement disorders.[2] The first local paediatric case was reported in 2009 in a 3-year-old girl, who presented with an encephalopathy and encephalitis lethargica–like illness after an upper respiratory tract infection.[3] The behavioural change in children may be difficult to recognise as they are fairly non-specific (eg irritability, hyperactivity, or temper tantrums). They can also have entailed non-psychiatric presenting features like seizures, dystonia, or verbal reduction.[2] Here we present yet another case with subtle, non-specific clinical symptoms that responded promptly to intravenous immunoglobulin. We believe this illustrates the importance of considering this uncommon differential diagnosis in the management of unexplained neurological conditions.

Case report

A 5-year-old girl presented to Prince of Wales Hospital in December 2010 with a low-grade increase in temperature (up to 37.5°C) for 5 days together with mild cough and a runny nose. She was more tired and "dull" than usual, for she received symptomatic treatment from private practitioner. Two days after the onset of upper respiratory symptoms, she manifested a fluctuating level of consciousness with markedly impaired speech and was admitted to our unit 3 days later. Her neurodevelopment was completely normal before onset of the illness and she enjoyed good past health. There was no history of recent travel or any contact who was sick. Her speech fluctuated, such that intermittently it appeared that she could only speak short sentences and mainly communicated by gesture or a babble of sounds. She cried easily and at times appeared frightened for no particular reason. Frequently, she also bit her own lips. She had no gastro-intestinal upset or seizures. On examination she appeared alert, but there was no spontaneous speech or appropriate verbal response. Apparently, she could recognise her parents and follow simple commands. However, most of the time she was irritable and did not cooperate when examined. Physical examination revealed a swollen lower lip attributed to self-inflicted trauma. There was no neck stiffness or focal neurological abnormality. Before this episode she was well toilet-trained, but on admission she could not indicate her toilet needs.

Initially she was managed for suspected encephalitis/central nervous system infection and received acyclovir and cefotaxime. During hospital stay her highest temperature was 37.5°C. Lumbar puncture showed raised cerebrospinal fluid (CSF) white cell count of 25 x 10^6 / L (70% polymorphs, 30% lymphocytes) with a protein level of 0.4 g/L (reference range: 0.15-0.45 g/L) and a glucose level of 4.1 mmol/L (paired plasma glucose level: 5.2 mmol/L). Bacterial cultures and viral studies by polymerase chain reaction and culture of CSF were negative. Her nasopharyngeal aspirate for respiratory viruses and *Mycoplasma pneumoniae* was negative. Brain computed tomography and

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contrast magnetic resonance imaging (MRI) were unremarkable. The electroencephalogram (both awake and sleep) showed intermittent slow delta waves over the posterior area (Fig), without any epileptiform discharges. Serum complement levels, thyroid function, paired viral titres, autoimmune screen, and urine for toxicology were all negative. After admission, her vital signs were stable. She remained alert and afebrile, though at times she was very irritable. There were no obvious problems with sleep, seizures, or dyskinesia. Clinically her main manifestations were mutism and irritability that persisted for a few days after admission. In view of the negative investigation results for central nervous system infection or epileptic encephalopathy, a possible immune-mediated encephalopathy was considered. She was therefore given intravenous immunoglobulin 1 g/kg/dose for 2 consecutive days. Her speech started to return after the first day of immunoglobulin treatment, and was able to count from 1 to 10 and name few familiar objects. The patient regained normal speech 1 week after finishing the immunoglobulin injections. Her CSF anti-NMDAR antibody was determined by recombinant immunofluorescence assay, and was found to be positive while that in blood was negative. Empirical screening for ovarian teratoma by ultrasound was negative. She returned to school 5 weeks since presentation and did not report any problem with speech, cognitive performance, or behaviour, and her mood became more stable. When she was followed up 3 months after discharge, she had made a complete recovery.

遇上原因不明的腦病可及早考慮抗NMDA受體腦炎的可能性

抗NMDA受體抗體的確認有助對抗NMDA受體腦炎臨床特徵的認識。雖然年輕患者出現腫瘤的機會較小，但抗NMDA受體腦炎近年在兒童身上愈見普遍，而常見的早期病徵包括行為和言語問題、抽搐和異常活動。本文報告一宗病徵輕微且不明的病例，並即時以靜脈內注射免疫球蛋白治療。我們相信這宗病例能說明醫護人員對治療原因不明的腦神經問題時，考慮這種異常鑒別診斷的重要性。

Discussion

After the first recognition of an antibody-mediated syndrome of memory deficits, psychiatric symptoms, decreased consciousness, and hypoventilation in four young women with ovarian teratoma in 2005,[4] they were subsequently identified as having the anti-NMDAR antibody.[1] Since then, the spectrum of anti-NMDAR encephalitis has been expanding. The condition is also increasingly recognised in children, though younger patients are less likely to have tumours, while behavioural and speech problems, seizures, and abnormal movements are common early presenting features.[5] These manifestations could be very 'non-specific' and very often patients were managed as if they had suspected encephalitis, especially if they were febrile or they had a history of non-specific upper respiratory tract illness. In a recent study of 203 patients with encephalitis who underwent extensive investigations, at least 4% of them had anti-NMDAR encephalitis, which was the second most common immune-mediated cause after acute disseminated encephalomyelitis. Nearly 20% of patients had immune-mediated causes,[6] which highlights the importance of immune-mediated processes in encephalitis-like presentations. With the rapid development in neuro-immunology, the spectrum of these diseases will expand. There is compelling clinical and laboratory evidence that anti-NMDAR antibodies are pathogenic. Hughes et al[7] showed that they cause a selective and reversible decrease in NMDAR surface protein, cluster density, and synaptic localisation that is associated with increased CSF and serum antibody

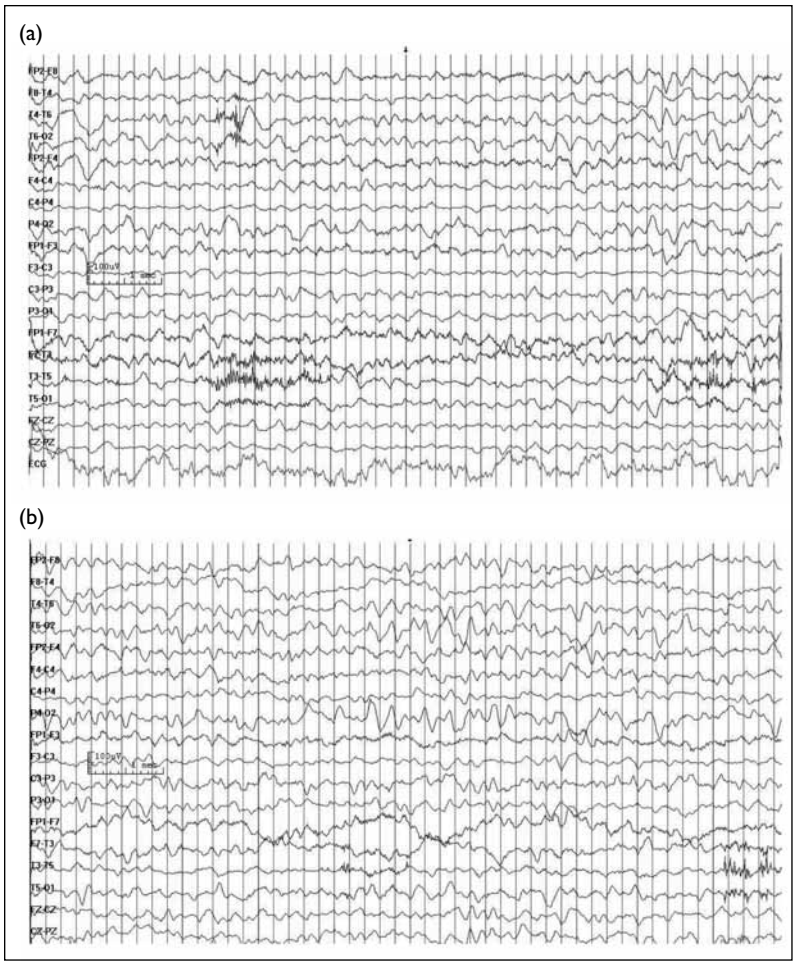

FIG. Electroencephalograms recorded on day 2 of admission when the patient was (a) awake and (b) asleep

titres. The reversibility of the disorder, irrespective of the duration of the symptoms, also suggests an immune-mediated neuronal dysfunction rather than an irreversible degeneration.[7] This is especially important in terms of management, such that physicians should not miss this potentially treatable condition. In fact, after the discovery of specific autoantibodies in relation to various forms of encephalitis, and the positive clinical response to early treatment with immunomodulatory agents, the diagnostic approach to diverse clinical problems has also changed. The original method for autoantibody detection described by Dalmau et al[1] used embryonic rat hippocampus neurons. Recently, recombinant immunofluorescence assay has been developed, validated, and become commercially available.[8] This test is currently available locally and may help to expand knowledge of this condition locally. In a recent review, Dalmau et al[2] suggested that for young patients in particular, anti-NMDAR encephalitis should be suspected in any individual who develops a rapid change of behaviour or psychosis, abnormal postures or movements (mostly orofacial and limb dyskinesias), seizures, and variable signs of autonomic instability. Brain MRI could be normal or shows transient fluid-attenuated inversion recovery or contrast-enhancing abnormalities. The CSF often reveals lymphocytic pleocytosis or oligoclonal bands. Anti-NMDAR antibodies should be checked in both CSF and serum.[2] First-line therapy of anti-NMDAR encephalitis consists of immunoglobulin and pulse methylprednisolone. Rituximab plus cyclophosphamide could be considered in refractory cases. Early treatment is associated with a better prognosis.[2] Since the turnaround time of the test takes a few weeks, the use of immunomodulating therapy needs to be considered before the availability of the results. Thus, a therapeutic trial with intravenous immunoglobulin and/or steroid may be undertaken, especially when common identifiable and treatable causes have been excluded, and the patient fails to improve or deteriorates rapidly.[9] Arguably, the patient's clinical improvement was 'too quick' and might have improved on its own, even without treatment, but it is also unfair to withhold treatment too long for fear of complications.

In summary, anti-NMDAR antibody detection in blood and CSF should be included as one of the initial investigations in unexplained acute or subacute encephalopathy, especially those with negative viral tests and poor clinical improvement. In affected patients, timely institution of immunomodulating therapy may have great prognostic implications for patient outcome.

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