A modern perspective on the differential diagnosis between encephalitis lethargica or anti-NMDA-receptor encephalitis

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ARTICLE INFO

Article history:
Received 24 July 2009
Accepted 12 January 2010

Keywords:
Anti-NMDA-receptor encephalitis
Encephalitis lethargica
NMDAR antibodies
Paraneoplastic syndrome

ABSTRACT

Two cases initially diagnosed as "encephalitis lethargica" are discussed. Both cases satisfied the published diagnostic criteria for encephalitis lethargica, with neuropsychiatric features including complex movement disorder, hypoventilation and altered conscious state. On later investigation N-methyl-D-aspartate receptor antibodies were detected in both cases. With the recent descriptions of tumour related antibodies to neuronal surface antigens in NMDA-receptor encephalitis, we highlight the importance of revisiting a diagnosis which may have prognostic significance.

1. Introduction

Encephalitis lethargica is defined as an acute or subacute encephalitic illness including at least three of the following criteria, where all other known causes of encephalitis have been excluded: (i) signs of basal ganglia involvement, (ii) oculogyric crises, (iii) ophthalmoplegia, (iv) obsessive-compulsive behaviour, (v) akinetic mutism, (vi) central respiratory irregularity, (vii) somnolence and/or sleep inversion.[1] We present two cases initially diagnosed with encephalitis lethargica [criteria (i), (vi), (vii)] who, on subsequent investigation, were demonstrated to be positive for N-methyl-D-aspartate receptor (NMDAR) antibodies.

2. Case 1

A 32 year old woman presented with a one week history of lethargy, headache, drowsiness, and paranoid delusions with perceptual distortions. The only medication use was the contraceptive pill. Physical examination was unremarkable. Investigations, including a delirium screen and magnetic resonance imaging (MRI) of the brain were normal, except for 10×10^6/L lymphocytes in the cerebrospinal fluid (CSF). She was treated with acyclovir, ceftriaxone and hydrocortisone covering for presumed infective encephalitis.

Over subsequent days she developed autonomic instability (tachycardias and labile blood pressure), dysphagia, aspiration pneumonia, and limb and orofacial dyskinesias. Repeat lumbar puncture was normal. MRI showed subtle pontine hyperintensities on T2-weighted MRI (Fig. 1).

On day 10 she was intubated for decreased conscious state and hypoventilation. Intravenous methylprednisolone (IVMP) and intravenous immunoglobulin (IVIG) were given without immediate effect. Dyskinesias increased, including upper and lower limbs. There were no obvious epileptic seizures noted and repeat EEGs demonstrated generalized slowing (theta/admixed delta) consistent with a diffuse cerebral disorder.

Further investigations were unremarkable for tumour markers (AFP; CA 125, 153, 19.9; CEA), paraneoplastic antibodies (Purkinje, Hu, Yo, Ri, CV2), autoimmune screen (including anti-thyroid antibodies), serology and viral PCR (for infectious encephalitides), and nutritional and metabolic screens. She was discharged from the intensive care unit (ICU) after seven weeks of prolonged cardiorespiratory support, with a further 2 months of inpatient rehabilitation. By nine months following initial presentation, she had regained functional independence and had returned to work (part time) as a business executive.

A year later, she again presented with two weeks of neuropsychiatric symptoms (delusions, anxiety, confusion, poor short-term memory, and word-finding difficulties) and autonomic instability. Physical examination was unremarkable. Peripheral white cell count was mildly abnormal (13.1×10^9/L). Orofacial dyskinesias were evident after the first week. Repeat investigations were normal. No epileptic seizures were noted; the EEG demonstrated slow background rhythm, predominantly in the fronto-temporal region. Treatment with IVMP followed by IVIG again did not appear to be effective.

Her clinical course during this second admission was less severe than her initial presentation and she was able to be managed with sodium valproate (for mood stabilization) and quetiapine, and did not require ICU admission. After 3 months inpatient management (rehabilitation included), she again returned home. At 6 months post discharge, she had returned to work as a corporate executive.

3. Case 2

A 22 year old woman presented with 8 days of frontal headache, agitation, short term memory loss and confusion. Physical examination was normal. Investigations (as for Case 1) were normal apart from CSF with 16×10^6/L lymphocytes. Brain MRI was unremarkable, whilst EEG showed non-specific slowing (bilateral delta waves) consistent with a diffuse cerebral disorder.

On day 2, she required intubation because of reduced conscious state and hypoventilation. Repeat MRI brain was unremarkable. She was commenced on empiric antiviral and antibiotic treatment. IVMP was also given without immediate effect.

By day 10 she developed orofacial and upper limb dyskinesias, and autonomic instability. She required 3 weeks of ICU, and returned home after 2 months of rehabilitation. Within 5 months from presentation, she returned to fulltime employment, leads a normal life (including international travel), and is symptom-free at 6 years.

3.1. Followup

In both cases followup screening for underlying malignancy was completed through the out-patient clinic, including CT chest/

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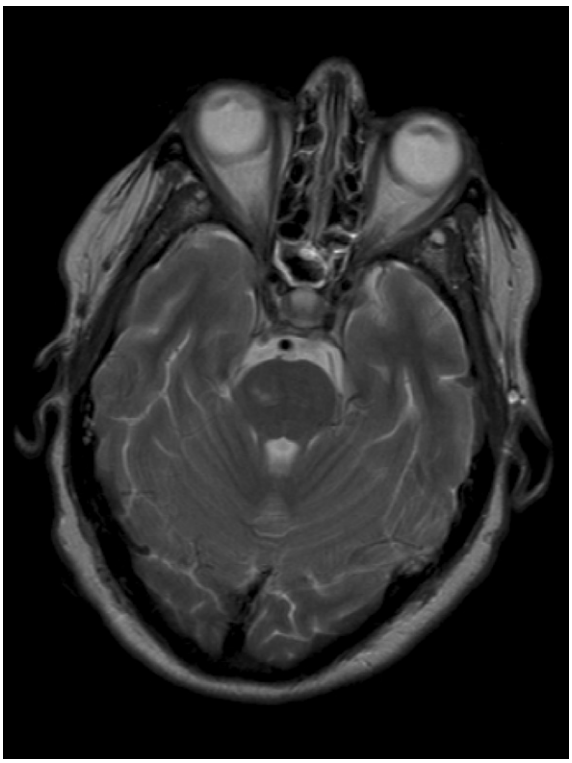

Fig. 1. Axial brain T2-weighted MRI showing subtle pontine hyperintensities.

abdomen/pelvis, and pelvic ultrasound. These investigations have been normal in both patients but ongoing screening is planned.

4. Discussion

The two cases described have complex neurological features and were initially diagnosed clinically as encephalitis lethargica, based on published criteria.[1] However, there is now a much better understanding of such cases with a rapidly growing literature on encephalitis with neuropsychiatric manifestations (psychiatric, extra-pyramidal, sleep and autonomic disturbances). In many such cases an association has been established with CSF and serum autoantibodies to the extracellular domain of the NR1/NR2 subunits of the N-methyl-D-aspartate receptor (NMDAR).[2–5] Indeed, many reports indicate that there is a correlation between NMDAR antibody titres and neurological outcome, suggesting a direct pathogenic role for the NMDAR antibodies.[6] This now represents a new category of immune-mediated neurological disorders (often paraneoplastic), and has led to greater understanding of the molecular mechanisms of encephalitis.[6]

The majority of adult and paediatric reported cases of NMDAR-antibody encephalitis are young women, with relapses reported in up to 15% of cases.[7,8] Awareness of NMDAR-antibody encephalitis is only relatively recent and as a consequence Case 1 was only tested at the time of her second admission, and Case 2 was tested when convalescent, two years after her initial presentation. However, serum and CSF were positive for NMDAR antibodies in both cases (NMDAR antibodies testing performed by Professor Josep Dalmau, University of Pennsylvania[6]).

Anti-NMDAR encephalitis is reported as having an association with tumours in 60% cases (most commonly teratomas).[6,7] Removal of these tumours significantly improves outcome, reducing ICU support time and likelihood of relapse.[9] No other specific aetiologies have been determined for the approximately 40% of cases that do not have an underlying tumour.[7] The two patients presented here were screened with CT chest/abdomen/pelvis, and pelvic ultrasound, to rule out malignancy. However, as some case reports have indicated that teratomas may only be identified years later, ongoing screening of these two patients is planned.[5]

Interestingly, the association of anti-NMDAR encephalitis with tumours appears less common in paediatric cases. Dale et al. studied the sera of 20 paediatric patients with a contemporary diagnosis of encephalitis lethargica and found positive sera for NMDAR Antibodies in only 50%; no tumours were identified in any cases.[8] From phenotypic analysis they concluded that the dyskinetic form of paediatric encephalitis lethargica is NMDAR-antibody positive, whereas those with Parkinsonism (akinesia/somnolence) are NMDAR-antibody negative. The two cases reported here (although not paediatric) had an extra-pyramidal movement disorders (dystonia/dyskinesia/chorea) as a prominent component of their clinical picture, tested positive for NMDAR antibodies, with no tumours identified despite extensive investigation.[3,5,10] Possibly those cases with the phenotype of a significant movement disorder may be less likely to have tumor as the aetiology.

MRI brain imaging is less reliable in NMDAR-antibody encephalitis. Only 55% of patients have been reported as having any FLAIR or T2 signal changes and, as noted in our two cases, there is little correlation with patient symptoms.[6] Reports of brain biopsies in NMDAR-antibody encephalitis similarly reveal little apart from some perivascular lymphocytes and microglial activation.[6] As in our two patients, recovery is typically slow with a persisting amnesia for a large period of the prehospital and hospital stay. Again, this aspect may link in with the disruption of the NMDA NR2B receptors which are predominately expressed in the forebrain and hippocampus.[6]

Various treatments have been used for anti-NMDAR encephalitis including steroids, intravenous immunoglobulins, plasma exchange, and rituximab but to date there has been no rigorous testing of these therapies in a randomised controlled trial.[7,11,12] Removal of an associated tumour is considered particularly effective and as such the presence of a teratoma may be considered a good prognostic factor, as it is potentially curable.[7,11,12]

5. Conclusion

We describe two patients previously diagnosed with encephalitis lethargica, who were subsequently demonstrated to have anti-NMDAR encephalitis. This report highlights the importance of reviewing previous clinical diagnoses of encephalitis with consideration given to serological antibody testing, and ongoing tumour screening. Although paraneoplastic encephalitis is generally associated with a poor prognosis, those associated with antibodies to neuronal surface antigens (NMDAR) generally have a much better prognosis, particularly with immunotherapy and removal of any tumours.

Acknowledgement

Professor Josep Dalmau, University of Pennsylvania, USA, kindly performed testing of CSF and sera for NMDAR antibodies.

References

1. Howard RS, Lees AJ. Encephalitis lethargica. A report of four recent cases. *Brain* 1987;**110**(Pt 1):19–33.
2. Tuzun E, Dalmau J. Limbic encephalitis and variants: classification, diagnosis and treatment. *Neurologist* 2007;**13**:261–71.
3. Dalmau J, Tuzun E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007;**61**:25–36.

4. Bataller L, Kleopa KA, Wu GF, et al. Autoimmune limbic encephalitis in 39 patients: immunophenotypes and outcomes. *J Neurol Neurosurg Psychiatry* 2007;**78**:381–5.
5. Iizuka T, Sakai F, Ide T, et al. Anti-NMDA receptor encephalitis in Japan: long-term outcome without tumor removal. *Neurology* 2008;**70**:504–11.
6. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008;**7**:1091–8.
7. Dale RC, Irani SR, Brilot F, et al. N-methyl-D-aspartate receptor antibodies in pediatric dyskinetic encephalitis lethargica. *Ann Neurol* 2009;**66**:704–9.
8. Dale RC, Church AJ, Surtees RA, et al. Encephalitis lethargica syndrome: 20 new cases and evidence of basal ganglia autoimmunity. *Brain* 2004;**127**(Pt 1):21–33.
9. Tuzun E, Zhou L, Baehring JM, et al. Evidence for antibody-mediated pathogenesis in anti-NMDAR encephalitis associated with ovarian teratoma. *Acta Neuropathol*.
10. Sansing LH, Tuzun E, Ko MW, et al. A patient with encephalitis associated with NMDA receptor antibodies. *Nat Clin Pract Neurol* 2007;**3**:291–6.
11. Schimmel M, Bien CG, Vincent A, et al. Successful treatment of anti-N-methyl-D-aspartate receptor encephalitis presenting with catatonia. *Arch Dis Child* 2009;**94**:314–6.
12. Ishiura H, Matsuda S, Higashihara M, et al. Response of anti-NMDA receptor encephalitis without tumor to immunotherapy including rituximab. *Neurology* 2008;**71**:1921–3.

doi:10.1016/j.jocn.2010.01.010

Atypical temporal arteritis causing posterior circulation stroke

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ARTICLE INFO

Article history:
Received 5 April 2009
Accepted 12 January 2010

Keywords:
Giant cell arteritis
Posterior circulation stroke
Stroke
Temporal arteritis

ABSTRACT

We report an 80-year-old woman presenting with a posterior circulation infarct secondary to temporal arteritis. The clinical and laboratory features were atypical. This case highlights the importance of having a low threshold for considering a temporal artery biopsy as accurate diagnosis, and prompt intervention may improve outcomes.

1. Case report

An 80-year-old woman presented with episodic gait disturbance on a background on six months of systemic symptoms. She had a past history of hypertension. Her systemic illness was dominated by myalgias and arthralgias with some associated weight loss. Three months prior to her presentation, her ESR was 49 mm/hr and her CRP was 90 mg/L. A presumptive diagnosis of polymyalgia rheumatica was made and a 7 day course of 25 mg prednisolone was given.

Two weeks after stopping this course, a fall occurred together with an episode of left sided weakness, left facial droop, dysarthria and diplopia lasting approximately 15 minutes. A CT brain revealed old cerebellar infarcts and duplex ultrasonography was normal. Over the subsequent weeks six further episodes of a similar nature occurred. After the final event, the symptoms failed to resolve, prompting her presentation to hospital. At no time had she had any headache, visual obscuration or jaw claudication.

Meanwhile, prednisolone had been recommenced at 7.5 mg bd then slowly weaned with improvement in the systemic symptoms.

On admission to hospital, the patient had a left sided Horner syndrome, left beating nystagmus, a partial left abducens palsy, dysarthria and prominent bilateral (left > right) cerebellar signs. An MRI and MRA was performed revealing acute infarction of the left pons and midbrain and severe vertebrobasilar disease (Fig. 1). Duplex ultrasound confirmed severely diminished flow in the posterior circulation. Inflammatory markers at the time of presentation revealed a CRP of 4 mg/L and an ESR of 20 mm/hour on 4 mg prednisolone daily.

Given the history of polymyalgia rheumatica together with the vertebrobasilar disease, a temporal artery biopsy was performed. This revealed a transmural lymphoplasmacytic infiltrate and multinucleated giant cells typical of giant cell arteritis (Fig. 2).

A treatment course of high dose oral corticosteroids was commenced and the patient underwent a successful rehabilitation program.

2. Discussion

Giant cell arteritis (GCA) or temporal arteritis (TA) is a chronic, granulomatous vasculitis of large and medium sized vessels occurring predominantly in patients over the age of 50 years. It is a common condition, but an uncommon cause of stroke, accounting for less than 1% of cerebral infarcts.[1] GCA is associated with neurological sequelae in approximately 30% of cases; this includes neuropathy, stroke, amaurosis fugax, neuro-otological problems, tremor, myelopathy and neuropsychiatric manifestations.[2]

The unusual features of this case are the atypical presentation and the essentially normal inflammatory markers. Although the patient had systemic symptoms, at no point did she have headache, visual disturbance, scalp tenderness or jaw claudication. This presentation is seen in approximately 10% of cases with biopsy proven temporal arteritis. However, these patients are usually

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