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New disease

Acute onset of focal seizures, psychiatric features and confusion: a case of autoimmune encephalitis?

Adam Al-Diwani,[1] Richard J Butterworth,[2,3] Anjan Nibber,[2] Bethan Lang,[2] Angela Vincent,[2] Sarosh R Irani[2]

[1]Medical Sciences Division, John Radcliffe Hospital, Oxford University Clinical Academic Graduate School, Oxford, UK
[2]Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford, UK
[3]Milton Keynes General Hospital, Milton Keynes, UK

Correspondence to Dr Sarosh R Irani, saroshirani@doctors.org.uk

Summary

An elderly woman presented with disorganised thinking, unusual behaviour and clustered episodes of speech arrest accompanied by right-sided face and arm twitching. The following investigations were normal: interictal electroencephalography, brain MRI, cerebrospinal fluid viral PCR and cell count and voltage-gated potassium channel-complex, *N*-methyl-D-aspartate receptor, gamma-aminobutyric acid (B) receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, glycine receptor, glutamic acid decarboxylase and paraneoplastic antibodies. The syndrome showed partial spontaneous resolution but 1 year later, typical postencephalopathic features persisted including disinhibition and alteration of sleep–wake cycle. The most likely clinical diagnosis was autoimmune encephalitis and the broader differential diagnoses are discussed within the article. This case demonstrates the need to be aware of this under-recognised and potentially treatable entity.

BACKGROUND

Autoimmune encephalitis caused by antibodies directed against central nervous system neuronal surface antigens is an increasingly recognised clinical entity. Depending on the antibody involved, patients may present with seizures, confusion, amnesia or psychiatric features. Autoimmune encephalitis is an important differential diagnosis to consider as neuropsychiatric outcomes correlate with time to immunosuppression. Furthermore, autoimmune encephalitis may be associated with an underlying tumour whose removal often expedites neurological recovery. While recently proposed diagnostic criteria emphasise ancillary antibody testing, a negative result should not exclude the diagnosis.[1] Here, we describe an abrupt onset of cognitive and behavioural disturbance with focal seizures that partially resolved without treatment. The patient tested negative for all known neuronal surface antibodies but the clinical features were most consistent with autoimmune encephalitis. Clinicians are reminded to have a high index of suspicion for this treatable and under-recognised disorder.

CASE PRESENTATION

A 77-year-old right-handed female active academic writer and researcher presented to the medical team. She had experienced a few days of disorganised thinking and frequent unilateral paroxysmal motor events associated with speech arrest and partial awareness. Her medical history consisted of recurrent epistaxis and hypertension, the latter was treated with bendroflumethiazide. She had no known personal or family history of neurological or psychiatric disorders.

Friends and family described a 2-week prodromal period during which she was 'not quite her usual self'. Normally lucid, she became more repetitive and found it difficult to engage with academic work at her usual level. She was fixated on the idea that her computer was broken but inspection by a technician suggested that the patient had used the computer in a manner that had inadvertently rendered it faulty. Her family described clusters of episodic involuntary right arm twitching accompanied by right facial twitching each lasting around 2 min. She was unable to speak during these episodes and only recalled half of the attacks. There was no evidence of physical illness in the preceding few weeks. None of the following features were present: fever, headache, weight loss, anorexia, night sweats, weakness, sensory disturbance, ataxia, hallucinations or persecutory, grandiose, obsessive or nihilistic thoughts.

On examination she was afebrile and haemodynamically stable. She scored 29/30 on a Mini Mental State Examination (MMSE). Neurological examination was otherwise normal. After a normal CT brain scan, a diagnosis of a stroke was made and she was discharged with aspirin and simvastatin.

On returning home, she placed an extensive collection of books into refuse bags and was intermittently disorientated to time. She piled books within a doorway appearing to barricade herself into a room. This precipitated re-admission, at which point a neurology referral was made. The only additional feature on examination was disinhibition. She did not believe she was suffering from an illness.

In retrospect, it was felt that the 2 min long episodes of right face and arm clonic jerking with speech arrest, occurring daily (around 5 times/day) were most consistent with a left frontal seizure focus.[2] However, these had now

disappeared. The co-occurrence of focal seizures and psychiatric features in a high-functioning previously well individual meant that an extensive differential diagnosis was considered. A thorough search for paraclinical evidence of encephalitis was undertaken.

INVESTIGATIONS

The following investigations were normal or unremarkable: urine dip, ECG, full blood count, urea and electrolytes, liver function, calcium, vitamin B12, thyroid function, C reactive protein, erythrocyte sedimentation rate, antinuclear antibody and antineutrophil cytoplasmic antibodies. Assays were negative for paraneoplastic antibodies (Hu, Yo, Ri, CV2, Ma2, Tr), antibodies directed against glutamic acid decarboxylase, thyroid peroxidase, the voltage-gated potassium channel (VGKC)-complex (including leucine-rich glioma inactivated 1 (LGI1), contactin-associated protein 2 (CASPR2) and contactin-2), and *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), gamma-aminobutyric acid (B) ($GABA_B$) and glycine receptors. A brain CT scan was normal. Cerebrospinal fluid (CSF) analysis showed two lymphocytes, no red cells, normal protein and glucose, normal cytology, negative herpes simplex virus PCR and no oligoclonal bands. Brain MRI (including diffusion weighted imaging, fluid attenuated inversion recovery, T1 and T2 sequences) showed moderate diffuse small vessel disease and the EEG showed a mild excess of left temporal slow waves: both were reported within normal limits for age but electrical activity contralateral to clonic motor seizure activity may be relevant. Whole body CT showed no evidence of an occult tumour.

DIFFERENTIAL DIAGNOSIS

The core features of this case are an acute onset of cognitive and behavioural disturbance with frequent, focal, spontaneously resolving seizures in a previously well and high-functioning elderly woman. Diagnoses considered included encephalitis, cerebrovascular disease, delirium, dementia, an intracerebral tumour and a primary psychiatric disorder.

The episodic motor features were gain, not loss, of function and were highly stereotyped, making seizures more likely than a vascular event. Ischaemia would account poorly for interepisode disorganised thinking, abnormal behaviour and spells of disorientation. However, subclinical cerebrovascular disease is the commonest cause of late-onset focal seizures[3] and was demonstrated on imaging, although no diffusion-weighted acute infarcts were seen. An acute confusional state (delirium) would explain both the cognitive and behavioural symptoms and, depending on its aetiology, the rapid onset. But there was no prominent disturbance of attention or orientation, and there was no obvious precipitant identified, such as infection or metabolic disturbance. Disinhibition and other psychiatric features have been reported as a feature of patients with frontal lobe epilepsy but these studies usually focused on patients with long-standing drug-refractory seizures.[4] The psychiatric features may be encountered in both dementia and a primary psychiatric disorder. The rapid onset and seizures may not be traditional presentations of dementia, however neurodegenerative conditions, such as Lewy body dementia and frontotemporal dementia may masquerade as subacute (1–6 weeks) onset presentations with fluctuations.[5] The presence of neurological features is not consistent with a primary psychiatric disorder. In addition, the first episode of a psychiatric disorder in the absence of a personal or family history in one's 70s is uncommon. While exclusion of a primary or secondary intracerebral tumour is important, the abrupt onset and the absence of associated focal signs made this unlikely.

Acute onset cognitive and behavioural symptoms coupled with focal seizures could represent autoimmune encephalitis, which may be paraneoplastic or, more commonly, non-paraneoplastic. However, many cases with autoimmune encephalitis described in the literature have abnormal MRI or CSF pleocytosis.[1] Other encephalitic aetiologies considered included toxic, metabolic (eg, Wernicke's) and infectious entities. The normal CSF results, coupled with no fever or headache, made an infectious encephalitis much less likely.

TREATMENT

As there was some clear spontaneous improvement in many of the features, and importantly no further seizures, possible immunological and symptomatic treatment options were discussed with the patient and her relatives, including medical doctors: the consensus view was that no specific treatments were indicated at this point.

OUTCOME AND FOLLOW-UP

At 2-months follow-up, several neuropsychiatric sequelae were noted. The patient reported vivid dreams, was more easily fatigued and had increased sleep requirements (from 7 to 12 h per night, including 2 or 3 h sleep in the afternoon). In addition, there were new disinhibited behaviours across many activities. For example, she was talking more freely and flight of ideas was noticeable. Repeat MRI (sequences, as above) was unchanged and both EEG and CSF were normal. After 1 year, these features have not improved and can be difficult for the family to manage. However, the patient was able to continue writing books, had no further seizures, her MMSE was 30/30 and Addenbrooke's Cognitive Examination—Revised (ACE-R) was 94/100.

DISCUSSION

As suggested by recent guidelines on the recognition of 'neuronal surface antibody-associated syndromes', the clinical features of both the presenting symptoms and postencephalitic picture combined with exclusion of other causes best fits with autoimmune encephalitis.[1] Autoimmune encephalitis is typically acute or subacute in the onset and is often associated with focal seizures, psychiatric features and usually an amnestic component, which was absent here. Proposed criteria require paraclinical tests to aid in confirmation of the diagnosis.[1]

Interest in this case focuses around the normality of imaging, EEG, CSF and serological studies and the spontaneous resolution of many symptoms. A few cases of seronegative autoimmune encephalitis have been reported previously[6 7] and in our opinion it is likely that our patient's disease was mediated by a novel antibody. This would not be surprising given the feast of novel antibodies against neuronal-surface proteins described in recent years. Potentially pathogenic antibodies against the

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VGKC-complex proteins LGI1, CASPR2 and contactin-2 and NMDA, glycine, $GABA_B$ and AMPA receptors are now recognised.[8] It has been proposed that other antibodies await discovery.[9]

Although the spectrum of phenotypes associated with these antibodies continues to expand[10 11] many clinical features are often distinctive. For example, patients with NMDAR-antibodies are typically young, show a psychiatric onset with seizures and commonly progress to develop a movement disorder and autonomic dysfunction.[8] By contrast, patients with VGKC-complex antibodies, typically directed against LGI1, show amnesia, a low serum sodium and the recently described syndrome of faciobrachial dystonic seizures (FBDS). FBDS are slightly different to the seizures in this patient as they are typically very brief (<3 s), very frequent (median of 50 times/day), associated with a dystonic, not clonic, movement and very rarely spontaneously remit. In fact, they are often refractory to multiple antiepileptic drugs.[12]

After discussion with the patient and her family, immunotherapies were not offered and there was some improvement without treatment. It is a matter of debate whether she should have received immunotherapy, but cases of spontaneous resolution are not without precedent.[6] Most of the evidence for current treatment protocols is based on case series and expert consensus rather than level 1–3 data. Therapies such as oral prednisolone, intravenous immunoglobulin and plasma exchange carry risks that should be weighed against expected benefits in disease remission.[13] Here, the observed complete spontaneous improvement in seizures and partial remission of cognitive features meant that risks were felt to outweigh benefits unless a relapse became apparent. However, the residual features seen in retrospect may suggest that steroid therapy was appropriate during acute presentation.

Some autoimmune encephalitides are a paraneoplastic process associated with an underlying malignancy: the rates vary based on the syndrome and the associated antibody. In most cases thorough screening for occult malignancy with CT-based structural imaging combined with functional scans such as positron emission tomography are required. Some authors recommend screening continue for at least 5 years following diagnosis.[1]

Our patient had a very high premorbid function. The residual disturbance in cognition and behaviour was one of the most troubling features particularly for friends, family and colleagues.[14] Although our patient feels very well in herself and follow-up to date shows no further seizures, her family feels she is very different, with episodes of impulsivity and emotional lability and a tendency to confabulate. The emerging view regarding persistent postencephalitic symptoms is that early immunosuppression correlates with positive neurological, cognitive and psychiatric outcomes. For example Finke *et al*[15] have described nine patients with proven NMDAR-antibody encephalitis where early immunosuppression predicted significantly better neuropsychological outcomes after a median of almost 4 years. As these authors point out, larger patient cohorts with focused cognitive follow-up will be required to better inform the prognosis and treatment options in this illness, an important matter for patients and the multidisciplinary team involved in their recovery.

Learning points

- Autoimmune encephalitis should be considered in abrupt or subacute disturbance of thoughts, cognition, memory and behaviour, especially if coupled with focal seizures.
- If autoimmune encephalitis is suspected it is important to consider the search for an occult malignancy.
- The treatment of non-resolving seronegative encephalitis involves immunosuppressive drugs.
- There are likely multiple undiscovered pathogenic antibodies underlying this disorder.
- The impact of postencephalitic sequelae must not be underestimated.

Competing interests AV and the Department of Clinical Neurology in Oxford receive royalties and payments for antibody assays. AV is the inventor on patent application WO/2010/046716 entitled 'Neurological Autoimmune Disorders'. SRI is a co-inventor. The patent has been licensed to Euroimmun AG for the development of assays for Lgi1 and other VGKC-complex Abs. AV and SRI may receive royalties for testing of VGKC-complex Abs.

Patient consent Obtained.

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