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TITLE OF CASE
Neuropsychiatric Systemic Lupus Erythematosus – a diagnostic challenge
SUMMARY
<p>A 58 year old woman presented to neuropsychiatric services with increased frequency of confusional episodes and intermittent psychotic symptoms. She had a 19 year history of atypical epileptic seizures and cognitive decline. Detailed review of past history and clinical investigations revealed that she had accumulated sufficient features to meet diagnostic criteria for systemic lupus erythematosus (SLE); she had previously had lymphopenia and a malar rash and she had positive anti-nuclear, anti-Ro and anti-SM antibodies, and elevated erythrocyte sedimentation rate. The seizures, cognitive impairment and psychosis were attributable to neuropsychiatric SLE. Treatment with immune-modulating therapy, cyclophosphamide, resulted in significant improvement in subjective and objective clinical presentation.</p> <p>Neuropsychiatric SLE should be considered a potential differential diagnosis for patients presenting with seizures, psychotic symptoms or cognitive decline. A detailed clinical evaluation with review of the medical history and appropriate laboratory analyses allows this diagnosis to be made, and appropriate treatment to be initiated.</p>
BACKGROUND
<p>Systemic lupus erythematosus (SLE) is an autoimmune disease in which the immune system reacts against host antigens resulting in dysfunction in various organ systems. The symptoms are often insidious in onset and non-specific in nature, making diagnosis difficult. Neuropsychiatric symptoms affect up to 90% of patients with SLE, with cognitive impairment, headache and mood disorder being the most commonly recognised syndromes[1].</p> <p>We present the case of a 58 year old woman who was diagnosed with SLE after a 19 year history of epilepsy and cognitive decline and responded well to immunotherapy.</p>
CASE PRESENTATION
<p>A 58 year old female Vietnamese former primary school teacher was admitted to a neuropsychiatric inpatient ward following increasingly frequent episodes of confusion and disorientation.</p> <p>She had originally been referred to Neuropsychiatric services in 1993 when she began to develop prolonged episodes of confusion which were thought to be psychogenic non-epileptic seizures. An electroencephalogram (EEG) following an episode in an outpatient clinic indicated postictal slowing leading to the diagnosis of focal epilepsy. She did not experience any typical clinical features of complex partial seizures.</p>

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She was lost to follow-up for many years and was re-referred to neuropsychiatry when the confusional episodes became more frequent. These episodes were now associated with headache, visual illusions, auditory hallucinations and persecutory ideas. A prolonged period of EEG monitoring in 2006 demonstrated runs of subclinical seizure activity, which correlated with her confusional state. Psychotic symptoms were considered to be related to post-ictal activity and antipsychotic medication (risperidone) was used to control these symptoms. Treatment also consisted of antiepileptic medication; therapeutic doses of a number of different medications were trialled with limited success in controlling her apparent seizures.

In 2010, she developed a malar facial rash and left shoulder pain which resolved spontaneously.

She was re-admitted to our inpatient neuropsychiatric unit in 2012 due to complaints from her family of worsening and increasingly frequent episodes of confusion and nocturnal enuresis which resulted in the need for 24 hour care. These episodes were now occurring on a daily basis. There was fluctuating conscious level but no overt motor seizure activity or psychotic symptoms.

She had well-controlled hypertension but no other chronic medical problems, did not drink alcohol and was a non-smoker. There was no evidence of Raynaud's Phenomenon.

Mental state examination revealed psychomotor agitation, reduced spontaneity of speech and prolonged speech latency and, although she was orientated in place, she was disorientated in time and unable to respond appropriately to questions about recent events. There was slowing of fine motor movements and reduced arm swing on walking and no other neurological deficit was noted.

INVESTIGATIONS

Detailed neuropsychological assessment, with a Vietnamese interpreter, demonstrated limited non-verbal reasoning, visual recall memory, executive function and speed of information processing, with relatively intact nominal and visuoperceptual skills. She had not undergone previous neuropsychological testing for comparison but these results suggested marked intellectual underfunctioning.

Twenty four hour ambulatory EEG did not show epileptiform activity, which contrasted with EEG in 2008, which had demonstrated sharp wave activity arising in the left parietal region. An MRI brain scan showed volume loss in the left medial temporal lobe, unchanged from serial imaging over the preceding ten years.

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Antinuclear antibody (ANA) was weakly positive at 1:40 and the extractable nuclear antigens (ENA), Anti-Ro and Anti-SM, were both positive. Anti-cardiolipin antibody was positive but other antiphospholipid antibodies were negative. Review of her clinical notes demonstrated that her ESR had been mildly raised in the past and she had previously been lymphopenic.

DIFFERENTIAL DIAGNOSIS

The history indicated that she met five of the American College of Rheumatology's (ACR) 11 clinical diagnostic criteria for systemic lupus erythematosus[2]:

- 1) Malar rash
- 2) Neurological disorder – psychosis and seizures
- 3) Haematological disorder – lymphopenia
- 4) Immunological disorder – positive ENAs, raised ESR.
- 5) Antinuclear antibody – positive

Clinical opinion was sought from a specialist in Neuroimmunology and it was agreed that a clinical diagnosis of neuropsychiatric SLE was likely. The initiation of relevant treatment was discussed in detail with the patient.

TREATMENT

Treatment with pulsed intravenous cyclophosphamide (15mg/kg, three weekly) was initiated, along with Mesna cover, to prevent cystitis. Due to a self-limiting episode of neutropenia after the first dose, the dose was reduced to 60% of its original level and continued on a three weekly basis until she had received three intravenous doses. Thereafter, the cyclophosphamide was converted to a three weekly pulsed oral cyclophosphamide regimen – seven additional treatments – which she tolerated without complications. Subsequently she was maintained on azathioprine 125mg daily.

OUTCOME AND FOLLOW-UP

Five months following the initiation of cyclophosphamide treatment, the patient was significantly less confused and demonstrated a marked improvement in social and cognitive function. She said that she felt better and her family described her as alert, more coherent and less drowsy. Episodes of nocturnal urinary incontinence resolved and she had become independent for self-care and been able to help out with domestic tasks. She showed an interest in puzzle games and current affairs.

Mental state examination showed her affect to be more reactive and there continued to be no psychotic or affective symptoms.

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Neuropsychological assessment at five months after initiation of cyclophosphamide demonstrated significant improvement from the previous assessment, with improved visual recall and non-verbal reasoning. Executive function and attention remained impaired.

Antipsychotic medication was gradually withdrawn without any problems and her antiepileptic medication reduced to Levetiracetam 1g BD and Gabapentin 600mg TDS. She has continued taking oral azathioprine as maintenance immunotherapy for the past 18 months.

DISCUSSION

This case of a 58 year old Vietnamese lady with a long history of atypical seizures, intermittent psychotic symptoms and progressive cognitive impairment demonstrates the value of vigilance for symptoms which indicate the diagnosis of neuropsychiatric SLE.

SLE has been described as the 'disease with a thousand faces'[3] due to the heterogeneity of clinical presentation, which often makes diagnosis difficult. In this case, the diagnosis had been delayed because of the unusual presentation of her symptoms. She was initially referred for suspected non-epileptic seizures as her confusional episodes did not clinically resemble complex partial seizures, with no automatisms. In addition to this, the protracted illness course with gradual accumulation of symptoms and biomarkers required for the diagnosis of SLE, rather than coexistence of these, resulted in the diagnostic challenge.

Revisiting the long history of the required diagnostic features allowed us to initiate a disease-modifying treatment for the neuropsychiatric SLE[4]. We postulate that the reduced frequency of confusional episodes reflecting subclinical seizures and significant improvement in cognitive function in our patient are attributable to the immunosuppressive effect of cyclophosphamide.

SLE is a chronic, relapsing-remitting systemic disease which is characterised by loss of immune tolerance, autoantibody production and immune complex deposition resulting in systemic inflammation. SLE is approximately four times more common in people of South East Asian ethnicity than White Caucasians[5], with a prevalence around 40/100,000[6], and mortality in this group is higher[5]. The preponderance of SLE in women is well established[7].

Prevalence estimates of neuropsychiatric symptoms in SLE varies according to how symptoms are defined. Studies have demonstrated prevalence of all symptoms around 90%[1], but when only major

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central nervous system (CNS) manifestations such as psychosis, myelopathy, strokes and seizures, are included and non-specific symptoms like headache and mild depression are excluded, prevalence falls to 4.3%[8]. In a case series of people with SLE, presence of antiphospholipid and anti-SM and -Ro antibodies were predictive of neuropsychiatric disease[9].

Neuropsychiatric symptoms of SLE have been divided by the ACR into CNS manifestations including cerebrovascular disease, cognitive dysfunction, seizures and psychosis, and peripheral nervous system disorders such as autonomic disorder, myasthenia gravis and mononeuropathies[10]. Neuropsychiatric symptoms of SLE are associated with generalised SLE activity and often recur[11]. The incidence of epilepsy in SLE is three times that of the general population and people with SLE and epilepsy are more likely to experience psychiatric disorders[12]. However, as in this case, seizures often predate other symptoms by many years and so diagnosis of isolated epilepsy syndromes is common[13]. Seizures commonly co-occur with cerebral atrophy[14].

Cognitive dysfunction in SLE can be associated with cerebral atrophy although markers of systemic disease involvement are not correlated with cognitive function[15]. It is a common neuropsychiatric feature of SLE, occurring to a mild or moderate extent in two-thirds of cases[16], although severe cognitive impairment is only seen in around 5% of people with SLE[11]. Cognitive dysfunction can occur in the early stages of the disease process but is rare[17] and, while cognitive function can deteriorate throughout the disease course, it often fluctuates or improves over time[18, 19]. The profile of cognitive deficits seen in SLE is varied but the most frequently affected domains are attention, memory, visuospatial processing, language, problem solving, speed of information processing and executive function[10]. The presence of cerebral atrophy, as was seen in this case, increases the risk of cognitive impairment[17].

Diagnosis of patients presenting with symptoms of neuropsychiatric SLE is challenging. Thorough medical history and clinical evaluation using relevant laboratory analyses aims to exclude other potential causes and attribute symptoms to SLE[20].

Although there is a paucity of high quality evidence on the management of neuropsychiatric symptoms of SLE, recommendations have been made on the basis of the available evidence. Treatment of cognitive dysfunction should include appropriate management of SLE and non-SLE associated factors, such as depression or physical ill-health. Non-pharmacological approaches such as cognitive rehabilitation programmes should also be considered. While long term anti-epileptic drug therapy is usually not

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indicated following a single seizure, recurrent SLE-related seizures should be managed using anti-epileptic therapy. Immunotherapy should be considered in systemic disease associated with seizures[11]. Individual case reports have also described response of psychiatric symptoms to immunotherapy[21].

LEARNING POINTS/TAKE HOME MESSAGES

- Neuropsychiatric symptoms are common in Systemic Lupus Erythematosus (SLE) but diagnosis can be difficult.
- The presence of atypical refractory symptoms, such as psychosis or seizures, should prompt diagnostic evaluation for neuropsychiatric SLE.
- Seizures often predate other neuropsychiatric symptoms of SLE, so vigilance for the subsequent emergence of other potential diagnostic criteria of SLE is important. These may not all occur at the same time.
- A robust and timely diagnosis of SLE allows management of symptoms, including symptomatic management, treatment of associated factors and consideration of immunotherapy.

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BMJ Case Reports

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