Taxing the brain: a case of neuropsychiatric systemic lupus erythematosus

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Introduction

The American College of Rheumatology defines neuropsychiatric systemic lupus erythematosus as an entity composed of 19 neuropsychiatric syndromes (Anonymous, 1999). Bortoluzzi et al (2015) have defined attribution criteria to help determine if symptoms are caused by active systemic lupus erythematosus, although there remains no diagnostic test. Neuropsychiatric systemic lupus erythematosus occurs in 10–15% of patients who have systemic lupus erythematosus, with a morbidity rate rivalling that of lupus nephritis (Hanly et al, 2007). This report describes a challenging diagnosis of neuropsychiatric systemic lupus erythematosus in an unusual case with evolving neuropsychiatric symptoms, without classical investigation findings for systemic lupus erythematosus disease activity.

Case report

The patient was a 42-year-old woman who presented with a 3-day history of generalised headaches and expressive dysphasia. Four weeks before her presentation, she noted polymyalgia, arthralgia and a malar rash (**Figure 1**). She had a background of hypothyroidism and systemic lupus erythematosus diagnosed 7 years ago, which was well controlled with hydroxychloroquine and steroids. Her examination was unremarkable excepting abnormal heel–shin gait. One day after admission, she experienced a tonic–clonic seizure accompanied by erratic temperature spikes up to 38.5 °C. No photophobia, neck stiffness or new rash was noted.

A differential diagnosis of ischaemic stroke, cerebral venous thrombosis, infectious or immune meningoencephalitis was considered. Loading dose aspirin, aciclovir, ceftriaxone, and levetiracetam were given. Full blood count, C-reactive protein level, urea and electrolytes, liver function tests, thyroid function tests and coagulation screen were normal. Glucose, magnesium, phosphate and calcium levels were within the normal range. Magnetic resonance imaging of the head revealed patent cerebral venous sinuses without ischaemia or haemorrhage and scattered high T2 foci within normal limits. Blood cultures were negative. CSF analysis showed normal glucose levels, opening pressure and lymphocyte count. The level of protein in the CSF was slightly elevated at 0.8 g/litre. No organisms were cultured or seen with Gram staining. No oligoclonal bands were noted. Screens for herpes simplex, varicella zoster, enterovirus, echovirus, syphilis, human immunodeficiency virus, tuberculosis, rubella, mumps, measles, Leishmania and Mycoplasma returned negative.

Her expressive dysphasia worsened, impairing her ability to speak in simple sentences. She became drowsier, with Glasgow Coma Scale scores decreasing to 13/15. Her antinuclear antibody levels were marginally raised at 1.2 units with an anti-ribosomal pattern. Erythrocyte sedimentation rate was minimally elevated at 20–30 mm/hr (but stable compared to baseline erythrocyte sedimentation rate of 20–22 mm/hr). Tests for anti-neutrophil cytoplasmic antibodies, anti-double-stranded-DNA (dsDNA) antibodies, anti-phospholipid antibodies, myositis antibodies, intrinsic factor antibodies, liver autoantibodies and lupus anticoagulant showed no abnormalities. Panels for anti-N-methyl-D-aspartate receptor (NMDAR), anti-leucine-rich glioma-inactivated 1, anti-contactin-associated protein 2, and anti-voltage gated calcium channel antibodies were negative. Complement levels were normal. Anti-Purkinje antibody studies revealed weakly positive anti-Yo antibodies. CSF flow cytometry, a whole body computed tomography scan, an abdominopelvic ultrasound scan and serum cancer biomarker levels were normal, making malignancy unlikely. She was treated for neuropsychiatric systemic lupus erythematosus with intravenous methylprednisolone. Her expressive dysphasia and Glasgow Coma Scale scores improved. She was given fortnightly cyclophosphamide pulses using the Eurolupus regimen and improved dramatically, in particular, completing full sentences and conversing.

How to cite this article:
Tan SYW, Zandi MS, Ellis S. Taxing the brain: a case of neuropsychiatric systemic lupus erythematosus. Br J Hosp Med. 2020. https://doi.org/10.12968/hmed.2020.0049

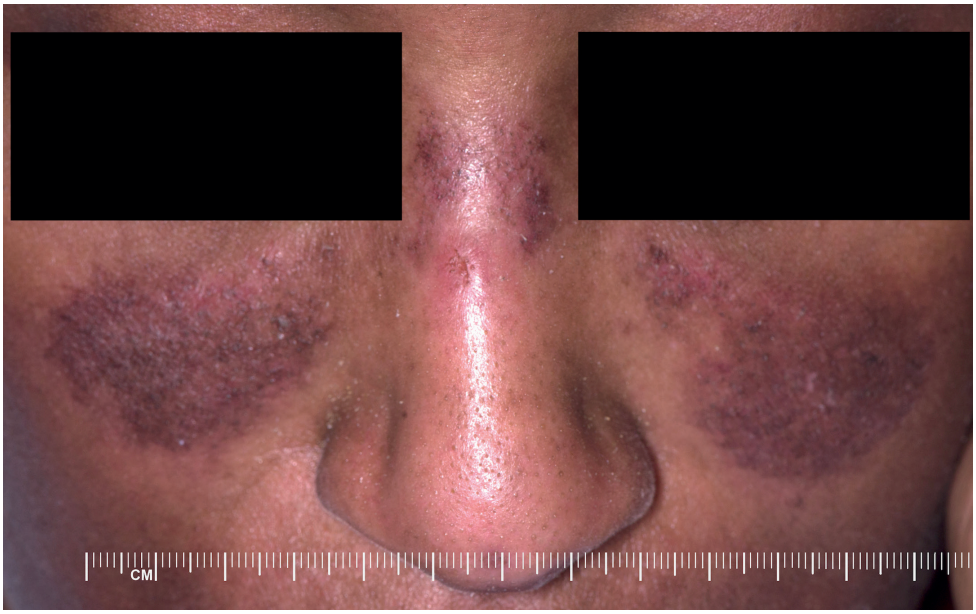

Figure 1. The malar rash that spread across the patient's cheeks while sparing the nasolabial folds, appearing 4 weeks before her admission. Photographs were taken when she first presented after headaches and expressive dysphasia were noted, and before she developed a tonic–clonic seizure.

Discussion

This is a rare case of neuropsychiatric systemic lupus erythematosus with evolving neuropsychiatric syndromes without typical biomarkers for a systemic lupus erythematosus flare. The neuropsychiatric syndromes described can be found in the American College of Rheumatology nomenclature system for neuropsychiatric systemic lupus erythematosus (Table 1) (Anonymous, 1999). The diagnosis of neuropsychiatric systemic lupus erythematosus was favoured for the following reasons:

- Negative findings for ischaemic stroke, cerebral venous thrombosis, CNS infections, autoimmune encephalitis or neoplasia
- Classic systemic lupus erythematosus malar rash preceding neurological symptoms
- Antinuclear antibody positivity
- Clinical improvement with methylprednisolone treatment.

Knowledge of autoantibodies associated with neuropsychiatric systemic lupus erythematosus can guide clinical decision making. Antiphospholipid antibodies and anti-aquaporin 4 antibodies cause focal events in systemic lupus erythematosus via thromboembolic phenomena (Schreiber et al, 2018) and initiating astrocyte cell death in a complement-dependent manner respectively (Verkman et al, 2013). Anti-dsDNA antibodies cross-reacting with NMDAR NR2 subunits may cause symptoms in neuropsychiatric systemic lupus erythematosus, although there are conflicting reports and this is not recommended as a clinically useful test (Aranow et al, 2010). Anti-ribosomal P antibodies have not been replicated or found to be pathogenic in systemic lupus erythematosus (Kiss and Shoenfeld, 2007). This patient was negative for common autoimmune encephalitis antibodies. Although an antibody-negative encephalitis syndrome was possible, her malar rash and active systemic lupus erythematosus makes neuropsychiatric systemic lupus erythematosus more likely.

An infectious or para-infectious process remains a possibility, as tests for other pathogens such as Leptospira bacterium or human herpes virus 6 were not conducted. Further testing and next generation sequencing would be recommended in refractory cases (Brown et al, 2018). Her Yo antibody raises the possibility of a paraneoplastic syndrome. While there was no evidence of malignancy, the authors recommend repeating testing of anti-Yo antibody levels for up to 5 years and requesting minimally invasive imaging if the antibody remained positive (Graus et al, 2016).

Without strict diagnostic criteria for neuropsychiatric systemic lupus erythematosus, skilled clinical judgement is required to establish a diagnosis. More sophisticated biomarkers

Table 1. American College of Rheumatology nomenclature system for neuropsychiatric systemic lupus erythematosus

Diffuse neuropsychiatric syndromes	Focal neuropsychiatric syndromes	
Central nervous system	**Central nervous system**	**Peripheral nervous system**
Psychosis	Headache	Acute inflammatory demyelinating polyradiculopathy
Anxiety disorder	Seizure disorders	Autonomic disorder
Acute confusional state	Cerebrovascular disease	Mononeuropathy – single or multiplex
Mood disorder	Movement disorders (chorea)	Plexopathy
Cognitive impairment	Myelopathy (aquaporin 4 or myelin oligodendrocyte glycoprotein antibody disease)	Polyneuropathy
	Demyelinating syndrome – neuromyelitis optica (aquaporin 4 and myelin oligodendrocyte glycoprotein antibody disease)	Myasthenia gravis
	Aseptic meningitis	Cranial neuropathy

From Anonymous (1999)

Table 2. The Systemic Lupus International Collaborating Clinics four factor attribution model

Item		Score
1. Time of the onset of neuropsychiatric event with respect to systemic lupus erythematosus clinical onset	Before (>6 months before systemic lupus erythematosus onset)	0
	Concomitant (within 6 months of systemic lupus erythematosus onset)	3
	After (>6 months after systemic lupus erythematosus onset)	2
2. Minor or not specific neuropsychiatric events as defined by Ainiala et al (2001)*	Present (ie minor or common neuropsychiatric events as proposed by Ainiala et al, 2001)	0
	Absent (ie neuropsychiatric events other than those proposed by Ainiala et al, 2001)	3
3. Confounding factors or not systemic lupus erythematosus-related associations as defined by the American College of Rheumatology glossary†	None or not applicable	2
	Present (one confounding factor)	1
	Present (more than one confounding factor)	0
4. Favouring factors†	None or not applicable	0
	Present (one additional or favouring factor)	1
	Present (more than one additional or favouring factor)	2

**Neuropsychiatric syndromes deemed as minor or common neuropsychiatric events include mild cognitive impairment, mild depression, headaches, anxiety and polyneuropathy without electrophysiological confirmation. †A full list of confounding and favouring factors is provided by Bortoluzzi et al (2015)*

in imaging, neurophysiology, and lab tests on spinal fluid and serum need development. Although an attribution model for ascribing neuropsychiatric events to systemic lupus erythematosus has been developed (Table 2) (Bortoluzzi et al, 2015), the diagnosis remains clinical, including exclusion of mimics.

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Learning points

- Neuropsychiatric manifestations of systemic lupus erythematosus can evolve rapidly and may mimic other forms of neurological pathology.
- Neuropsychiatric systemic lupus erythematosus may occur without typical investigation findings suggesting systemic lupus erythematosus disease activity.
- Diagnosis of neuropsychiatric systemic lupus erythematosus can be difficult, and should be made using logical clinical reasoning, especially in the absence of clear biomarkers for a systemic lupus erythematosus flare.
- New diagnostic tools and improved biomarkers are needed to guide clinicians, as there are currently no defined diagnostic criteria for neuropsychiatric systemic lupus erythematosus.

Conflicts of interest
Michael S Zandi has received honoraria for lecturing from Eisai and UCB; Sean YW Tan and Spencer Ellis declare no conflicts of interest.

Acknowledgements
Michael S Zandi is supported by the UCLH/UCL National Institute for Health Research Biomedical Research Centre.

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