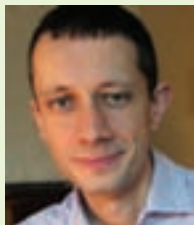


Advances and Challenges in Neuropsychiatric Systemic Lupus Erythematosus



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Systemic lupus erythematosus is a common autoimmune disease (4.71 per 100,000 age-standardised incidence in the UK in the 1990s),^{1,2} and many lupus patients have heterogeneous neurological and psychiatric symptoms (collectively termed neuropsychiatric or NP 'events'; see table) at some point in their lives. But is this neuropsychiatric lupus (NPSLE), and is NPSLE one, two or many diseases? Research criteria and attempts at classification of NPSLE have been overly inclusive, which has set back the field.³ For example, in these criteria, headache is generally attributed to lupus and is the most common manifestation, but careful analysis of published data shows no association between headache and lupus.⁴ Underpinning the clinical heterogeneity is pathological heterogeneity. I shall argue that it is useful to split the pathology into two groups. First, symptoms and signs due to antibody-mediated and inflammatory pathology, and second, collectively, the rest: cerebrovascular disease, low mood, anxiety, migraine, or functional symptoms (of course, this second group has a natural divide between vascular disease and the others). The latter collective group is far more prevalent, and the distinction between groups important because of treatment implications. Cerebrovascular disease is arguably the most important manifestation of NPSLE, but requires conventional preventative therapy, and is not likely to respond to immunotherapy. In contrast, antibodies or inflammation may cause some forms of myelopathy, psychosis, seizures and epilepsy, and thus immunosuppression may work (although with which drug is as yet unclear). Thus, we need markers to distinguish between these two groups, as such an aetiological classification is likely to prove more useful in diagnosis and therapy than a neuroanatomical one.

Recent modifications to the 1999 American College of Rheumatology criteria for NPSLE have moved the criteria forward in this regard (summarised in the table). In these modifications, laid out by the Systemic Lupus International Collaborating Clinics (SLICC) group, neurological symptoms and signs are attributed to or not to lupus on the basis of severity, exclusion of mimics and temporal relation to lupus diagnosis (without acknowledgment of aetiology).^{5,8} This already cuts a 40% prevalence of NPSLE to 13% using the most stringent criteria in the largest prospective study, but more needs to be done.⁸ In this brief

review I shall summarise the current understanding of the pathogenesis of NPSLE, progress in the search for markers of immunotherapy-responsive forms, and the evidence base for therapy. The figure below gives a timeline of selected clinical and immunological advances.

Pathogenesis

Let us consider lupus generally and then NPSLE. Lupus, like multiple sclerosis, is a complex genetic trait. Genome wide association studies have started to add risk loci to multiple regions within HLA, complement components and other genes already known to confer risk.⁹ A current model is of multiple paths to lupus, with a general 'compromise' of innate and adaptive immunity.¹⁰ A critical number of 'hits' may be required before disease develops. There are defects in clearance of apoptotic cellular debris; activation of innate mechanisms which sense DNA and other nuclear material; and B and T cell over-activity.¹⁰ For CNS disease, rare monogenic forms of lupus with striking CNS associations may provide clues. Inherited complement component C1q deficiency is rare but associated with a severe CNS vasculitis, the mechanism of which is uncertain.¹¹ There are many reports of antibodies in lupus sera binding to neurons *in vitro*.¹² The rare childhood encephalopathy Aicardi-Goutières Syndrome is due to mutations in the gene for DNA three prime repair exonuclease 1, *TREX1*, and is associated with high CSF levels of interferon-alpha (IFN α) and serological markers typical of lupus.¹³ This, together with the type 1 IFN peripheral blood signature seen in active lupus,¹⁴ and a lupus-like cognitive syndrome seen in patients with Hepatitis C or melanoma treated with IFN α ,¹⁵ provides sufficient support for a study of the role of IFN α in CNS lupus. Antibodies and cytokines may therefore have a role in the pathogenesis of some forms of NPSLE. See the figure for a summary of animal models which support this.

Pathological and serological studies show that ischaemia is the main pathology, but less common antibody mediated mutations also exist. The neuropathological studies from the 1970s and 1980s paint a picture of vasculopathy, infection, and infarction - with vasculitis a rarity.^{16,21} Other studies, limited generally by the choice of control group, suggest that subcortical, white matter lesions (see later) are linked to the cognitive deficits of lupus, and associated with sustained

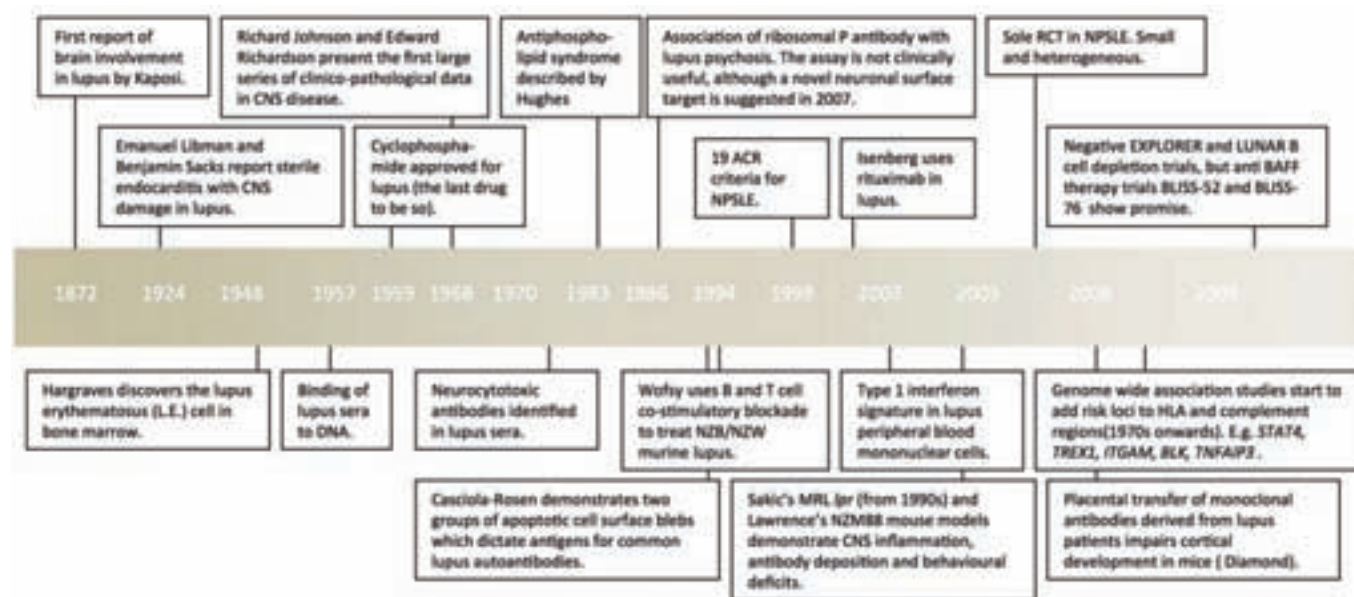


Figure: Timeline of selected clinical (top) and immunological (bottom) developments.

Abbreviations. ACR, American College of Rheumatology. BAFF, B cell activating factor. BLISS-52 and -76, A Study of Belimumab in Subjects With Systemic Lupus Erythematosus (52 and 76 week studies). *BLK*, B lymphoid tyrosine kinase gene. CNS, central nervous system. EXPLORER, A Study to Evaluate the Efficacy and Safety of Rituximab in Patients With Severe Systemic Lupus Erythematosus. *ITGAM*, integrin alpha M. *lpr*, lymphoproliferation gene. LUNAR, A Study to Evaluate the Efficacy and Safety of Rituximab in Subjects With ISN/RPS Class III or IV Lupus Nephritis. MRL, murine lupus. NPSLE, neuropsychiatric lupus. NZB/NZW, New Zealand Black/New Zealand White. NZM88, New Zealand mixed strain 88. RCT, randomised controlled trial. *STAT4*, signal transducer and activator of transcription 4 gene. *TNFAIP3*, tumor necrosis factor alpha-induced protein 3 gene. *TREX1*, three prime repair exonuclease 1 gene. References are not given due to space limitations.

and high titre cardiolipin antibodies (which are not specific to CNS disease).^{22,23} Atherosclerosis is accelerated in lupus.²⁴ Vascular damage may well account for many neurological symptoms, especially in long-standing disease. But this is not the whole story. It is now well-accepted that myasthenia gravis,²⁵ and some forms of longitudinally extensive transverse myelitis (LETM) and recurrent optic neuropathy (aquaporin-4 antibody associated)²⁶ are associated with lupus. For the latter, aquaporin-4 immunity may explain some cases of myelopathy in lupus and Sjögren's. In a recent series, all six lupus patients with LETM and both of the two with recurrent optic neuritis possessed aquaporin-4 antibodies.²⁶ For common manifestations such as seizures (42% of 41 patients in a recent retrospective series from southwestern England and south Wales, in which visual failure and movement disorders were also prominent²⁷), the pathology therefore may be ischaemic damage in the majority, but in some the same phenotype may be due to pathogenic antibody (see below).

Finding a marker of immunotherapy-responsive NPSLE

Antibodies hold the most promise as markers of forms of NPSLE, as SLE is characterised by their abundance. The discovery of aquaporin-4 immunity in lupus and Sjögren's disease has shed light on the nature of myelopathy in these conditions, which has yet to happen for other forms of NPSLE because no antibody has been found. Meanwhile, the evidence that antibodies to native forms of neuronal channels can cause various forms of encephalitis has been reproduced by several groups (See Vincent update, ACNR 10.1).²⁸ Studies of neu-

Table. Evolving research classifications of neuropsychiatric lupus (NPSLE)

<p>1. American College of Rheumatology (ACR) 1999 case definitions of neuropsychiatric lupus: the 'NP events'.³</p> <p>Central nervous system</p> <p>Aseptic meningitis Cerebrovascular disease Demyelinating syndrome Headache (including migraine and benign intracranial hypertension) Movement disorder (chorea) Myelopathy Seizure disorders Acute confusional state Anxiety disorder Cognitive dysfunction Mood disorder Psychosis</p> <p>Peripheral nervous system</p> <p>Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome) Autonomic disorder Mononeuropathy, single/multiplex Myasthenia gravis Neuropathy, cranial Plexopathy Polyneuropathy</p> <p><small>'exclusions' and 'associations' for the above found here: http://www.rheumatology.org/publications/ar/1999/aprilappendix.asp (accessed 30 Mar 2010)</small></p>	<p>2. Systemic Lupus International Collaborating Clinics (SLICC) attribution models, 2007.⁶</p> <p>strict model 'A'</p> <ol style="list-style-type: none"> 1. use ACR 'exclusions' and 'associations' 2. exclude cases which fall out of an enrollment window up to six months prior to diagnosis of SLE and up to 15 months after diagnosis 3. exclude "minor" neuropsychiatric events (Ainiala): all headache, anxiety, 'mild' cognitive dysfunction (<3 domains), polyneuropathy unconfirmed by nerve conduction studies and electromyography. <p>modified model 'B'</p> <p>As above, but a 10-year window prior to diagnosis of SLE is allowed, and use of ACR 'exclusions' but not 'associations'.</p> <p>3. Published SLICC results so far:</p> <p>2008, antibody associations. For 214 events in 133 of 412 patients (32.3%) (model A: 32/214, model B: 77/214), there was no strong association between NP events, however attributed, and anti-ribosomal P, DWEYS-NR2 (see text), lupus anticoagulant (LAC), cardiolipin, and 2-glycoprotein I antibodies measured at variable times after the NP event. However, a suggestive signal exists for ribosomal P and psychosis, and LAC and cerebrovascular disease.⁷</p> <p>2010, outcome. For 843 events in 486 of 1206 (40%) patients (model A: 149/843, model B: 258/843), attributable events occur early and have a favourable outcome compared to non-attributable events. A therapeutic window?⁸</p>
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ropil encephalitis and variants have shown that cell surface antigens are the only ones likely to be clinically meaningful,²⁸ but in lupus the literature is full of intracellular targets with soft associations. A couple of candidates have come close. Antibodies to ribosomal protein subunits have been variably reported in lupus psychosis, and one group

has reported a novel neuronal surface antigen to which some of these antibodies cross-react, though this study has not been replicated.²⁹ Some lupus ds-DNA antibodies have been reported to cross react with a short peptide sequence, DWEYS, on the NR2a and NR2b subunits of the NMDA receptor (long before recognition of NMDAR encephalitis³⁰), but rou-

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Precautions Inform patients of most common adverse reactions. Use with caution in patients with previous or current depressive disorders and those with antecedents of suicidal ideation. Advise patients to report immediately any symptoms of depression and/or suicidal ideation. Closely monitor patients exhibiting depression and treat appropriately. Consider cessation of therapy. Administer with caution in patients with a history of seizures and those receiving anti-epileptics, particularly if epilepsy is not adequately controlled. Closely monitor patients with cardiac disease for worsening of their condition during initiation of therapy. Patients should use an aseptic injection technique and rotate injection sites to minimise risk of injection site necrosis. If breaks in skin occur, patients should consult their doctor before continuing injections. If multiple lesions occur, discontinue Rebif until healed. Use with caution in patients with history of significant liver disease, active liver disease, alcohol abuse or increased serum ALT. Monitor serum ALT prior to the start of therapy, at months 1, 3 and 6 and periodically thereafter. Stop treatment if icterus or symptoms of liver dysfunction appear. Treatment has potential to cause severe liver injury including acute hepatic failure. Full haematological monitoring is recommended at months 1, 3 and 6 and periodically thereafter. All monitoring should be more frequent when initiating Rebif 44µg. New or worsening thyroid abnormalities may occur. Thyroid function testing is recommended at baseline and if abnormal every 6–12 months. Use with caution in, and closely monitor patients with, severe renal and hepatic failure or severe myelosuppression. Serum neutralising antibodies may develop and are associated with reduced efficacy. If a patient responds poorly and has neutralising antibodies, reassess treatment. Use with caution in patients receiving medicines with a narrow therapeutic index cleared by cytochrome P450. Women of childbearing potential should use effective contraception. Limited data suggest a possible increased risk of spontaneous abortion. During lactation, either discontinue Rebif or nursing. If overdose occurs, hospitalise patient and give supportive treatment. **Side effects** In the case of severe or persistent undesirable effects, consider temporarily lowering or interrupting dose. **Very common:** flu-like symptoms, injection site inflammation/reaction, headache, asymptomatic transaminase increase, neutropenia, lymphopenia, leucopenia, thrombocytopenia, anaemia. **Common:** injection site pain, myalgia, arthralgia, fatigue, rigors, fever, pruritus, rash, erythematous/maculo-papular rash, diarrhoea, vomiting, nausea, depression, insomnia, severe elevations of transaminase. **Serious side effects include:** injection site necrosis, hepatitis with or without icterus, severe liver injury, anaphylactic reactions, angioedema, erythema multiforme, erythema multiforme-like skin reactions, seizures, thromboembolic events, thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, suicide attempt, Stevens-Johnson syndrome, dyspnoea, retinal vascular disorders. Consult the Summary of Product Characteristics for more information relating to side effects. **Legal category** POM. **Price** Rebif 8.8µg and 22µg: 6 (0.2ml) + 6 (0.5ml) syringes – £552.19; Rebif 22µg: 12 syringes (0.5ml) – £624.77; Rebif 44µg: 12 syringes (0.5ml) – £813.21; Rebif 8.8µg/0.1ml and 22µg/0.25ml: 2 cartridges – £406.61; Rebif 22µg/0.5ml: 4 cartridges – £624.77; Rebif 44µg/0.5ml: 4 cartridges – £813.21; For prices in Ireland, consult distributors Allphar Services Ltd. **Marketing Authorisation Holder and Numbers** Merck Serono Europe Ltd, 56 Marsh Wall, London, E14 9TP. EU/1/98/063/007; 003; 006; 010; 008; 009. **For further information contact:** UK: Merck Serono Ltd, Bedford Cross, Stanwell Road, Feltham, Middlesex, TW14 8NX. Tel: 020 8818 7373. **Republic of Ireland:** Merck Serono, 3013 Lake Drive, Citywest Business Campus, Dublin 24. Tel: 01 4661910. **Date of Preparation** January 2010.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. In the Republic of Ireland information can be found at www.imb.ie. Adverse events should also be reported to Merck Serono Limited - Tel: +44(0)20 8818 7373 or email: medinfo.uk@merckserono.net.

Date of Preparation: March 2010

REB10–0057

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1. PRISMS Study Group. *Lancet* 1998;**352**:1498–1504.
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time serological testing has not proved to be useful, due to lack of specificity.^{7,21} Conversely, only one patient in the published data so far from patients with neuropil encephalitis, with AMPAR antibodies, has had lupus serology, namely dsDNA antibodies. But, this patient was not given a diagnosis of lupus and also had a thymic carcinoma, which was the probable driver of AMPAR antibody.³² It is probably the strategies used by groups working on neuropil encephalitis, including proteomic approaches, that will discover cell surface antigens in lupus.³³

What is the role of brain imaging? In a diagnostic work-up, brain imaging (and CSF examination) is done first to exclude other pathology, principally vascular or infection, including progressive multifocal leucoencephalopathy (PML) which was on the scene long before the biological therapeutics era.^{34,35} Small white matter lesions in lupus are common, non-specific and may reflect ischaemic damage. One small study by Appenzeller in a Brazilian population revealed some correlation of such lesions (present in roughly half of the patients studied) in time with steroid dosage, cardiopilin antibodies, or previous neurological symptoms.²³ A few studies have revealed white matter atrophy and altered neurometabolic profiles on spectroscopy in patients with lupus, correlating with cognitive dysfunction.³⁶ So although imaging seems unlikely to offer a diagnostic test for immunotherapy responsive NPSLE, it has use in longitudinal follow up of vascular disease and in the detection of PML.

SLE as a differential diagnosis in neurology

SLE features among many lists of differential diagnoses in neurology, and the serological tests now available can be misleading. Antinuclear antibody (ANA) and double stranded DNA (dsDNA) antibody tests are both problematic. ANA is over-sensitive and positivity is common in the general population, in particular with increasing age. dsDNA antibody is much more specific for lupus but less sensitive, and absolute levels are not useful in monitoring response to therapy.³⁷ A good rule of thumb when faced with a discordant ANA result in a neurology clinic, without clinical features of systemic lupus, is to ignore it at first. Antiphospholipid syndrome (either primary or secondary to lupus) is an important diagnosis that can mimic multiple sclerosis, and the presence of sustained high titre phospholipid antibodies are useful in diagnosis.

Treatment

There is no clear evidence base for the treatment of NPSLE. However, to put this in context, neither is there a standard of care in lupus nephritis, which is more common and better studied. Achieving sustained remission with minimal steroid usage is the ultimate goal. There remains just one published randomised controlled study in NPSLE – a small study in which 18 of 19 patients treated with intravenous schedules of cyclophosphamide responded compared to 6 of 13 in the methylprednisolone group.³⁸ But, the case mix of NPSLE manifestations (mainly seizures, transverse myelitis and peripheral neuropathy) and the differences between the groups make firm conclusions from this study difficult to make. Well designed retrospective studies exist, and show that intensive immunotherapy is probably a good thing. The University College London group have reported 10 of 11 cases of lupus psychosis from a 485 patient cohort, in whom a variety of treatments including steroids, plasmapheresis, cyclophosphamide and azathioprine were used. Most of the patients had a good long term outcome with no recurrence, particularly if treated aggressively.³⁹ The best controlled studies of immunosuppression in lupus have been in nephritis, and support the use of low-dose-cyclophosphamide, azathioprine, and mycophenolate mofetil (MMF). Ten-year follow up data from the Euro-lupus nephritis trial reveals that low dose cyclophosphamide followed by azathioprine is effective at inducing and maintaining sustained remission.⁴⁰ MMF is probably as effective as cyclophosphamide in inducing remission in nephritis, but safer.⁴¹

B cell depletion therapy, with the monoclonal chimeric anti-CD20 antibody, rituximab, has had the most promising open label data in the last few years, for refractory lupus in particular. The drug appears effective in open studies of refractory severe NPSLE^{42,43}, but there have been no randomised controlled trials. Two phase III trials in which severe NPSLE was an exclusion criterion (EXPLORER,⁴⁴ all lupus; and LUNAR,



nephritis) have shown no increased efficacy of rituximab over conventional treatment. This could be due to inclusion of mild disease, fixed 'damage', and concomitant immunosuppression usage.⁴⁵ One should be alert to the risk of PML after rituximab, but this seems small.³⁵ Another B cell centred agent, belimumab, a monoclonal antibody which inhibits B-cell activating factor (BAFF), suffered similar negative results at phase II, but after rigorous trial re-design has recently had success (in all lupus, but again with CNS lupus excluded) in phase III studies, BLISS-52 and BLISS-76.⁴⁶ The consensus among rheumatologists who have led these studies is that trial design may have let rituximab down. But even the very basics of trial design in NPSLE have not yet been achieved.

So, having excluded infection and vascular pathologies, a pragmatic treatment approach is to use steroids, followed by plasmapheresis or intravenous immunoglobulin if the disease manifestation seems antibody-mediated (e.g. LETM, and possibly psychosis), for induction of remission,

and then azathioprine or MMF for maintenance therapy. Cyclophosphamide or rituximab are reserved for severe refractory disease. Warfarin is used for thrombotic events associated with the antiphospholipid syndrome, but the intensity and duration of therapy remains unclear.⁴⁷

Conclusion

NPSLE is heterogeneous, and current classification criteria are misleading. We need a marker that distinguishes immunotherapy-responsive disease from ischaemic, infectious or other aetiologies. One marker exists for LETM and optic neuritis in lupus: aquaporin-4 antibodies. There is a small evidence base for therapy of NPSLE, which suggest, for carefully selected cases, initial treatment with steroids followed by MMF or azathioprine. Cyclophosphamide and rituximab are reserved therapies for severe refractory disease. ♦

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