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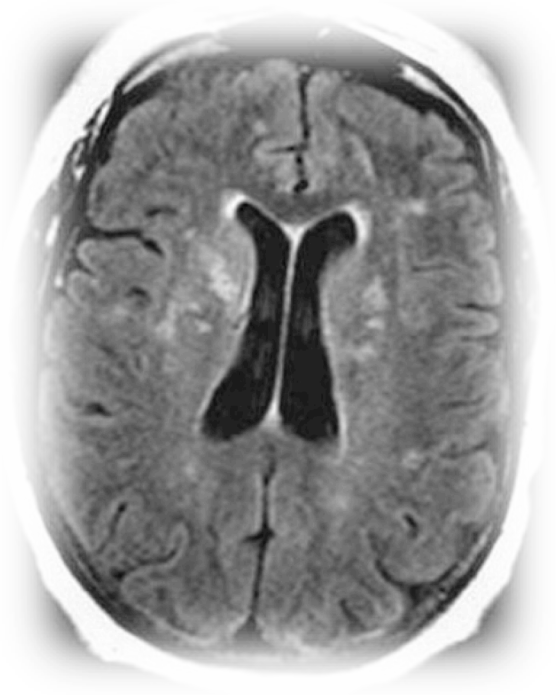
Neuropsychiatric systemic lupus erythematosus in two European centres: Clinical and neuroimaging characteristics, treatment options and comparison of usual care with the EULAR recommendations

Μελέτη της φυσικής ιστορίας, γενετικών και ανοσολογικών παραμέτρων στο συστηματικό ερυθηματώδη λύκο: Νευροψυχιατρικός λύκος



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ΔΙΔΑΚΤΟΡΙΚΗ ΔΙΑΤΡΙΒΗ

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SUMMARY

Introduction

Neuropsychiatric systemic lupus erythematosus (NPSLE) poses a diagnostic and therapeutic challenge. An American College of Rheumatology (ACR) research committee has published a set of case definitions for 19 NPSLE syndromes, in an effort to homogenize terminology for research and clinical practice purposes. These case definitions involve both the central and the peripheral nervous system, are categorized into focal and diffuse and have a wide heterogeneity that ranges from overt manifestations such as stroke, seizures and psychosis, to headache or cognitive dysfunction. Attribution of neuropsychiatric events to lupus warrants a thorough investigation and exclusion of alternative causes. Diagnostic workup and treatment decisions are typically performed on a patient-by-patient basis and often necessitate the involvement of multiple medical specialties. In an effort to homogenize the management of patients with NPSLE, a EULAR task force has issued a set of recommendations addressing diagnostic and therapeutic issues, using a combination of evidence-based approach and expert consensus. A validation or comparison of these recommendations with routine clinical practice has not been performed.

One particular neuropsychiatric manifestation included in the ACR nomenclature for NPSLE is demyelinating syndrome (termed lupoid sclerosis in the past). However, distinction of this entity from frank multiple sclerosis (MS) is not clear, given the recent advances in MS diagnostics, which aim to increase sensitivity in diagnosing the disease.

Aims of the Thesis

For the purpose of this Thesis, we performed a comprehensive study of NPSLE in two European centres (with the cooperation of a EULAR scholar, Dr. Cristina Pamfil from «Iuliu Hatieganu» University of Pharmacy and Medicine, Cluj-Napoca, Romania). More specifically we:

- analyzed demographic, clinical and neuroimaging data from all “primary” NPSLE cases from Heraklion and Cluj
- compared routine clinical practice against the EULAR recommendations for NPSLE to unveil potential pitfalls and limitations
- evaluated treatment options and long-term outcome of NPSLE - analyzed in more detail patients that received cyclophosphamide (CYC) for severe neuropsychiatric manifestations, using a structured approach to assess response
- identified SLE patients with clinical and neuroradiological features of demyelination and classified them as SLE-associated demyelinating syndrome or coexistence of SLE with frank MS, by diagnostic criteria.

Patients and methods

Two national tertiary referral centres for patients with SLE and suspected neuropsychiatric involvement, Heraklion, Greece and Cluj, Romania participated in the study.

- For the characterization of the NPSLE cohort, SLE patients with confirmed "primary" neuropsychiatric involvement were selected by retrospective chart review from all lupus cases over the last 15 years. All patients fulfilled at least four of the revised American College of Rheumatology (ACR) classification criteria for SLE at the time of NPSLE diagnosis and had undergone regular follow-up in each centre. For each neuropsychiatric manifestation included, we recorded all diagnostic procedures the patients underwent and the therapies they received. We then compared the diagnostic and therapeutic decisions applied, against the EULAR recommendations for NPSLE (both the general ones and those specific to the event).
- To assess the efficacy and safety profile of CYC in NPSLE, we identified "primary" NPSLE cases that received CYC for their neuropsychiatric syndrome and documented all variables relating to dosing, route of administration and cumulative dose, outcome and duration of follow-up, as well as occurrence of serious adverse events.
- For the characterization of patients with SLE and demyelinating features, we scrutinized our NPSLE cohorts and also utilized data from the independently established cohort of MS in the Neurology Clinic of the University Hospital of Heraklion, to identify potential patients with features of both diseases. Identified cases were followed up with combined rheumatologic/neurologic evaluation on a regular basis at 3–6 month intervals, depending on disease activity. We also reviewed the English language literature using the PubMed database from 1966 to January 2013 with the following index terms: "multiple sclerosis" OR "myelitis" OR "myelopathy" OR "demyelination" AND "SLE" OR "lupus" (terms present in title or abstract).

Results

- *Characterization of the NPSLE cohort and comparison of usual clinical care with the EULAR recommendations*: We identified 94 patients who experienced a total of 123 lupus-related neuropsychiatric events. Approximately 35% of events occurred within the first year after SLE diagnosis. Most prevalent events were cerebrovascular diseases (CVD) (n=21, 17.1%), cognitive dysfunction (n=18, 14.6%), intractable lupus headache and mood disorder (n=12 each, 9.8%).

Brain MRI was performed in 75 neuropsychiatric events (61.0%). In 21 of them (28.0%), MRI was considered normal; in the remaining cases, the most common finding was non-specific periventricular white matter hyperintensities (WMHIs, 40.8%), followed by cerebral infarcts (21.1%). Treatment included steroids (either initiation or escalation of previous dose) in 89 cases (72.4%) and immunosuppressives in 73 cases (59.3%). Antithrombotic therapy was administered in 41 neuropsychiatric events, most commonly in ischemic CVD.

We found overall satisfactory concordance rates between usual care and the EULAR recommendations, with level of agreement reaching 68.7% for diagnostic work-up and 62.7% for treatment decisions. In a *post-hoc* analysis, we did not observe statistically significant differences in terms of agreement with the EULAR recommendations, when neuropsychiatric events were stratified according to the time period (prior to or after 2010, year of publication of the EULAR recommendations) they occurred. Despite this good concordance, we identified a number of issues such as overutilization of brain MRI (42.9% of neuropsychiatric events with no such recommendation), suboptimal evaluation for cognitive dysfunction (less than 30% of patients underwent formal neurocognitive assessment) and frequent use of immunosuppressives in CVD disease (52.4% of cases received immunosuppression in addition to antiplatelets/anticoagulants).

- *Efficacy and safety of CYC for NPSLE*: CYC was administered in 50 neuropsychiatric events. Most frequent indications were psychosis (12 cases), polyneuropathy (6 cases), and cerebrovascular disease, seizure disorder and cranial neuropathy (5 cases). CYC was mainly administered as monthly pulses (median number: 8.0, median cumulative dose: 7.2 gr). Cases were followed for a median of 46.5 months. At last follow-up, partial or complete response of NPSLE was observed in 84% of events; 10% had stable disease, whereas the remaining 6% failed to improve or worsened and were rescued with rituximab. Relapses were observed in six events (12%) at median 8 months after initial response. No malignancies were observed, yet there were three cases of severe infections. Amenorrhea was recorded in three patients, who had not received gonadal protection.

- *Characterization of SLE patients with demyelinating features*: Our cohort of NPSLE patients included patients with myelopathy and optic neuropathy, however no patients qualified for the ACR definition of SLE-associated demyelinating syndrome. On the contrary, scrutinization of both SLE and MS cohorts identified nine patients who fulfilled the diagnostic criteria for both SLE and MS. This corresponded to prevalence rate 1.0-1.2% in each cohort. (SLE and MS). Initial presentation of MS included spinal symptoms in seven patients. All patients had features of mild SLE with predominantly cutaneous, mucosal and musculoskeletal manifestations. Accordingly, therapeutic decisions were mainly guided by the severity of the neurological syndrome. During median follow-up of 4 years, three patients remained stable and the remaining experienced gradual deterioration in their neurological status. SLE remained quiescent in all patients while on standard immunomodulatory MS therapy.

The systematic literature search identified detailed reports of nine cases of SLE and MS coexistence. Unlike our patients who carried a mild SLE phenotype, cases from the literature tended to have more severe SLE, with three patients having at least one major manifestation including CNS, renal, and severe hematologic disease.

Conclusions

We characterized the cohorts of NPSLE patients in two European experienced centres and attempted to juxtapose real-life management of SLE patients with neuropsychiatric manifestations with the EULAR recommendations, and identify areas that may require additional attention. Notably, the time period of our study predominantly included events that occurred before the publication of the EULAR recommendations in 2010. In this regard, the overall good concordance rates between usual care and the recommendations and the absence of a significant difference in this concordance between events occurring prior and after publication of the recommendations is a reassuring observation, as the management of NPSLE has traditionally been based on expert opinion. Nevertheless, despite good concordance between EULAR recommendations for NPSLE and usual clinical practice, we identified a number of issues such as overutilization of brain MRI, suboptimal evaluation for cognitive dysfunction and frequent use of immunosuppressives in cerebrovascular disease that need to be further investigated.

Regarding the efficacy of CYC in NPSLE, our observations confirm the efficacy of pulse CYC inthis situation, since more than 80% of events demonstrated at least moderate improvement from their baseline status during the follow-up period. Our finding of higher response rates in cases where CYC was given as 1st line therapy could imply that intense immunosuppression is more efficacious if instituted early in NPSLE. Not withstanding the retrospective nature of our data, in cases wherein gonadotoxicity is not a major concern, pulse CYC should not be withheld in severe NPSLE.

Finally, we did not find cases of "demyelinating syndrome" in our cohort of NPSLE patients. Instead, using our hospital-based SLE and MS cohorts at the University of Crete, we identified patients with SLE who additionally fulfilled the diagnostic criteria for MS and described the prevalence, diagnosis, treatment, and prognosis of cases that have both diseases. We found that coexistence of the two disorders reaches an estimated point prevalence of about 1% among patients with SLE or MS. The combination of these findings suggests that, given the high sensitivity of new diagnostic criteria for MS, the concept of "MS-like" syndrome in SLE may need to be reevaluated, since it may actually represent overlap of two diseases. Patients with SLE-MS overlap in our experience tend to have mild SLE without major extra-CNS organ involvement, which does not require intensive immunosuppressive treatment. MS tends to follow a relapsing-remitting course (frequent relapses), yet with minimal accumulation of disability and its clinical severity dictates the choice of immunomodulating agents.

ΠΕΡΙΛΗΨΗ

Εισαγωγή

Οι ασθενείς με συστηματικό ερυθηματώδη λύκο (ΣΕΛ) παρουσιάζουν 9.5 φορές αυξημένο κίνδυνο για νευροψυχιατρικές εκδηλώσεις σε σχέση με το γενικό πληθυμό (**νευροψυχιατρικός ΣΕΛ, ΝΨΣΕΛ**). Σε προοπτικές μελέτες, η συχνότητα εμφάνισης νευροψυχιατρικών εκδηλώσεων κυμαίνεται 40–50% σε ασθενείς ΣΕΛ με Καυκάσια ή Ισπανική καταγωγή και 10–20% σε ασθενείς με Ασιατική καταγωγή. Η ονοματολογία του American College of Rheumatology (ACR) ορίζει **19 διαφορετικά νευροψυχιατρικά σύνδρομα** σε ασθενείς με ΣΕΛ που αφορούν είτε το *κεντρικό νευρικό σύστημα* (ΚΝΣ), όπως είναι η άσηπτη μηνιγγίτιδα, η ψυχωτική διαταραχή, και η επιληπτική διαταραχή, είτε το *περιφερικό νευρικό σύστημα* (ΠΝΣ), όπως είναι η πολυνευροπάθεια και η αυτόνομη νευροπάθεια. Τα νευροψυχιατρικά σύνδρομα διαχωρίζονται επίσης σε *εστιακά*, όπως το αγγειακό εγκεφαλικό σύμβαμα και η μυελοπάθεια και σε *διάχυτα*, όπως η άνοια και η οξεία σύγχυση. Στη χώρα μας δεν έχει μελετηθεί επαρκώς η επιδημιολογία του νευροψυχιατρικού ΣΕΛ, καθώς και η διαγνωστική-θεραπευτική προσέγγιση των ασθενών αυτών.

Η διαγνωστική προσέγγιση και η θεραπευτική αντιμετώπιση του ΝΨΣΕΛ αποτελεί μια κλινική πρόκληση και τυπικά γίνεται σε εξατομικευμένη βάση με τη συμμετοχή πολλαπλών ιατρικών ειδκοτήτων (ρευματολόγος, νευρολόγος, ψυχίατρος, νευροαπεικονιστής). Σε μια προσπάθεια να ομογενοποιηθεί η αντιμετώπιση των ασθενών με ΝΨΣΕΛ, η Ευρωπαϊκή Εταιρεία Ρευματολογίας (European League against Rheumatism, EULAR) θέσπισε το 2010 κατευθυντήριες οδηγίες για τη διάγνωση και τη θεραπεία της συγκεκριμένης κλινικής οντότητας, χρησιμοποιώντας συνδυασμό των υπαρχόντων βιβλιογραφικών δεδομένων (evidence-based) και της γνώμης μιας μεγάλης ομάδας ειδικών (expert opinion). Η εφαρμογή των συγκεκριμένων κατευθυντήριων οδηγιών δεν έχουν δοκιμαστεί/επαληθευτεί στην καθημερινή κλινική πράξη.

Ένα από τα 19 διαφορετικά κλινικά σύνδρομα του ΝΨΣΕΛ είναι το απομυελινωτικό σύνδρομο (παλαιότερη ονομασία: «λυκοειδής σκλήρυνση» (lupoid sclerosis). Παραταύτα, η διάκριση του συνδρόμου αυτού από την πολλαπλή σκλήρυνση (ΠΣ) (multiple sclerosis, MS) δεν είναι σαφής, δεδομένης της πρόσφατης προόδου στη διαγνωστική της ΠΣ, η οποία στοχεύει στην αύξηση της ευαισθησίας και ειδικότητας στη διάγνωση της ΠΣ.

Σκοπός της μελέτης

Για το σκοπό της παρούσας διατριβής, πραγματοποίησαμε μια αναλυτική μελέτη/καταγραφή του ΝΨΣΕΛ σε δύο ευρωπαϊκά τριτοβάθμια κέντρα (με τη συνεργασία της Δρ. Cristina Pamfil από το Πανεπιστήμιο Φαρμακολογίας και Ιατρικής «Iuliu Hatieganu», στο Cluj-Napoca της Ρουμανίας.

Πιο συγκεκριμένα:

- αναλύσαμε δημογραφικά, κλινικά και νευροαπεικονιστικά δεδομένα από όλες τις περιπτώσεις ΝΨΣΕΛ στο Ηράκλειο και το Cluj
- συγκρίναμε την καθημερινή κλινική πρακτική με τις κατευθυντήριες οδηγίες της EULAR για το ΝΨΣΕΛ για να αποκαλύψουμε πιθανές πρακτικές αδυναμίες των τελευταίων
- αξιολογήσαμε τις θεραπευτικές επιλογές και την έκβαση των ασθενών με ΝΨΣΕΛ - αναλύσαμε σε βάθος την αποτελεσματκότητα και την ασφάλεια της ενδοφλέβιας κυκλοφωσφαμίδης (CYC) σε περιπτώσεις σοβαρού ΝΨΣΕΛ, χρησιμοποιώντας μια δομημένη (structured) προσέγγιση για την αξιολόγηση της κλινικής ανταπόκρισης των ασθενών
- αναγνωρίσαμε ασθενείς με ΣΕΛ και κλινικοαπεικονιστικές εκδηλώσεις απομυελίνωσης, ταξινομώντας τους ως «απομυελινωτικό σύνδρομο σχετιζόμενο με ΣΕΛ» ή ως συνύπαρξη ΣΕΛ και ΠΣ, με βάση τα υπάρχοντα διαγνωστικά κριτήρια.

Ασθενείς και μέθοδοι

Δύο περιφερειακά τριτοβάθμια κέντρα αναφοράς για ασθενείς με ΣΕΛ και πιθανή ΝΨ συμμετοχή συμμετείχαν στη μελέτη (Κλινική Ρευματολογίας, Κλινικής Ανοσολογίας και Αλλεργίας, Πανεπιστημιακό Νοσοκομείο Ηρακλείου, Ελλάδα - Τμήμα Ρευματολογίας, Πανεπιστήμιο Φαρμακολογίας και Ιατρικής «Iuliu Hatieganu», Cluj-Napoca, Ρουμανία.

- Για το χαρακτηρισμό της κοορτής ΝΨΣΕΛ, όλοι οι ασθενείς με ΣΕΛ και επιβεβαιωμένη «πρωτοπαθή» ΝΨ συμμετοχή ανασκοπήθηκαν με αναδρομική μελέτη όλων των φακέλων των ασθενών με ΣΕΛ τα τελευταία 15 έτη. Όλοι οι ασθενείς πληρούσαν ≥ 4 από τα αναθεωρημένα κριτήρια ταξινόμησης του ACR για τη διάγνωση του ΣΕΛ τη στιγμή της ΝΨ εκδήλωσης και είχαν τακτική παρακολούθηση σε ένα από τα κέντρα της μελέτης. Για κάθε ΝΨ εκδήλωση που συμπεριλήφθηκε, καταγράψαμε όλες τις διαγνωστικές πράξεις και τις θεραπείες που χρησιμοποιήθηκαν. Στη συνέχεια, συγκρίναμε τις διαγνωστικές και θεραπευτικές αυτές αποφάσεις με τις αντίστοιχες οδηγίες της EULAR για το ΝΨΣΕΛ (γενικές και ειδικές οδηγίες).
- Για την εκτίμηση της αποτελεσματικότητας και του προφίλ ασφάλειας της CYC στο ΝΨΣΕΛ, συμπεριλάβαμε περιπτώσεις ΝΨΣΕΛ που έλαβαν CYC ως θεραπεία και καταγράψαμε όλες τις παραμέτρους σχετικά με τη δοσολογία, οδό χορήγησης και συνολική δόση, τελική έκβαση και διάρκεια παρακολούθησης, καθώς και την εμφάνιση τυχόν σοβαρ.ων ανεπιθύμητων ενεργειών.
- Για το χαρακτηρισμό των ασθενών με ΣΕΛ και απομυελινωτικές εκδηλώσεις, επανεξετάσαμε τις κοορτές ΝΨΣΕΛ και επιπλέον χρησιμοποιήσαμε δεδομένα από την ανεξάρτητη κοορτή ΠΣ της Νευρολογικής Κλινικής του Πανεπιστημιακού Νοσοκομείου Ηρακλείου. Οι ασθενείς που ανευρέθηκαν παρακολουθήθηκαν με συνδυασμένη ρευματολογική και νευρολογική επίσκεψη κάθε 3-6 μήνες, ανάλογα με την ενεργότητα των νοσημάτων. Επιπλέον, ανασκοπήσαμε την Αγγλική βιβλιογραφία, χρησιμοποιώντας τη βάση δεδομενων PubMed από το 1966 ως τον Ιανουάριο 2013 και τους ακόλουθπυς όρους: “multiple sclerosis” OR “myelitis” OR “myelopathy” OR “demyelination” AND “SLE” OR “lupus” (όροι παρόντες στον τίτλο ή την περίληψη).

Αποτελέσματα

- *Περιγραφή της κοορτής ΝΨΣΕΛ και σύγκριση της καθημερινής κλινικής πρακτικής με τις οδηγίες της EULAR*: Συμπεριλήφθηκαν 94 ασθενείς με 123 συνολικά ΝΨ εκδηλώσεις αποδιδόμενες στων ΣΕΛ. Οι πιο συχνές εκδηλώσεις ήταν τα αγγειακά εγκεφαλικά επεισόδια (ΑΕΕ) (n=21, 17.1%), η γνωσιακή δυσλειτουργία (n=18, 14.6%), η "αποδιδόμενη στο λύκο" κεφαλαλγία και οι διαταραχές της διάθεσης (n=12 το καθένα, 9.8%).

Μαγνητική τομογραφία (MRI) εγκεφάλου πραγματοποιήθηκε σε 75 ΝΨ εκδηλώσεις (61.0%): σε 21 από αυτές (28.0%) ήταν φυσιολογική, ενώ στις υπόλοιπες, το συχνότερο εύρημα ήταν οι μη-ειδικές στικτές βλάβες της λευκής ουσίας (WMHIs, 40.8%), ακολουθούμενες από τα εγκεφαλικά έμφρακτα (21.1%). Η θεραπεία περιλάμβανε γλυκοκορτικοειδή (έναρξη ή αύξηση προηγούμενης δόσης) σε 89 περιπτώσεις (72.4%) και ανοσοκατασταλτικά φάρμακα σε 73 (59.3%). Αντιθρομβωτική αγωγή χορηγήθηκε σε 41 ΝΨ συμβάματα, κατά κύριο λόγο σε περιπτώσεις ισχαιμικών ΑΕΕ.

Βρήκαμε συνολικά ικανοποιητικό επίπεδο συμφωνίας μεταξύ της καθημερινής κλινικής πρακτικής και των οδηγιών της EULAR, με ποσοστά σύμπτωσης 68.7% για τις διαγνωστικές πράξεις και 62.7% για τις θεραπευτικές αποφάσεις. Σε μεταγενέστερη (*post-hoc*) ανάλυση, δε βρήκαμε στατιστικά σημαντικές διαφορές στη συμφωνία με τις οδηγίες, ανάλογα με το έτος εμφάνισης κάθε ΝΨ εκδήλωσης (δλδ. πριν ή μετά το 2010, έτος έκδοσης των οδηγιών της EULAR). Παρά το συνολικά ικανοποιητικό επίπεδο συμφωνίας, αναγνωρίσαμε ορισμένες σημαντικές διαφοροποιήσεις, οι χαρακτηριστικότερες των οποίων είναι: i) η υπερβολική χρήση της MRI εγκεφάλου στην κλινική πρακτική (42.9% των ΝΨ εκδηλώσεων χωρίς να υπάρχει συγκεκριμένη οδηγία), ii) η μη λεπτομερής αξιολόγηση της γνωσιακής λειτουργίας (λιγότερο από το 30% των ασθενών με δυσλειτουργία υποβλήθηκαν στην ενδεδειγμένη λεπτομερή νευροψυχολογική αξιολόγηση) και iii) η σχετικά συχνή χρήση ανοσοκατασταλτικών σε περιπτώσεις ΑΕΕ (52.4% έλαβαν ανοσοκατασταλτικά επιπρόσθατα της αντιαιμοπεταλιακής/αντιπηκτικής θεραπείας).

- *Αποτελεσματικότητα και ασφάλεια της CYC στο ΝΨΣΕΛ*: Χορηγήθηκε CYC σε 50 ΝΨ εκδηλώσεις, συχνότερες των οποίων ήταν: ψύχωση (11 περιπτώσεις), πολυνευροπάθεια (6 περιπτώσεις) και ΑΕΕ, επιληπτικές κρίσεις και κρανιακές νευροπάθειες (5 περιπτώσεις έκαστη). Η CYC χορηγήθηκε κυρίως ως μηνιαίες ενδοφλέβιες ώσεις (διάμεσος αριθμός ώσεων: 8, διάμεση συνολική δόση: 7.2 γρ). Η διάμεση διάρεια παρακολούθησης ήταν 46.5 μήνες. Στην πλέον πρόσφατη εκτίμηση, πλήρης ή μερική ύφεση των ΝΨ συμπτωμάτων παρατηρήθηκε σε 84% των εκδηλώσεων· 10% είχαν σταθεροποίηση των συμπτωμάτων, ενώ το υπόλοιπο 6% εμφάνισε επιδείνωση και έλαβαν «θεραπεία διάσωσης» με rituximab. Υποτροπές της αρχικής ΝΨ εκδήλωσης παρουσιάστηκαν σε 6 περιπτώσεις (12%) σε 8 μήνες (διάμεση τιμή) μετά την αρχική ανταπόκριση. Δε βρέθηκαν περιπτώσεις κακοήθειας, υπήρξαν όμως 3 περιπτώσεις σοβαρών λοιμώξεων. Τρεις ασθενείς ανέπτυξαν αμηνόρροια, ως απόρροια της μη λήψης προστασίας γονάδων κατά τη θεραπεία με CYC.

- *Χαρακτηρισμός ασθενών με ΣΕΛ και απομυελινωτικές κλινικές εκδηλώσεις*: Παρά την ύπαρξη ασθενών με μυελοπάθεια ή οπτική νευροπάθεια στην κοορτή ασθενών με ΝΨΣΕΛ, κανένας ασθενής στην εν λόγω κοορτή δεν πληρούσε τα ACR κριτήρια για το «απομυελινωτικό σύνδρομο σχετιζόμενο με ΣΕΛ». Αντιθέτως, η ανάλυση των κοορτών ασθενών ΣΕΛ και ΠΣ αναγνώρισε εννέα ασθενείς που πληρούσαν τα κριτήρια για τη διάγνωση τόσο του ΣΕΛ όσο και της ΠΣ (επιπολασμός για κάθε κοορτή: 1.0-1.2%). Το αρχικό κλινικό σύνδρομο της ΠΣ περιλάμβανε συμπτώματα από το νωτιαίο μυελό σε επτά ασθενείς. Όλοι οι ασθενείς είχαν ευρήματα ήπιου ΣΕΛ με δερματοβλεννογόνιες και μυοσκελετικές εκδηλώσεις κατά κύριο λόγο. Ως εκ τούτου, οι θεραπευτικές αποφάσεις καθοδηγήθηκαν κυρίας από τη σοβαρότητα της νευρολογικής συνδομής. Κατά τη διαρκεία της 4-ετούς παρακολούθησης (διάμεση τιμή), τρεις ασθενείς παρέμειναν σταθεροί και οι εναπομείναντες εμφάνισαν σταδιακή επιδείνωση του νευρολογικού στάτους τους. Ο ΣΕΛ παρέμεινε σε χαμηλή ενεργότητα ή ύφεση σε όλους τους ασθενείς.

Η συστηματική ανασκόπηση της βιβλιογραφίας ανέδειξε εννέα περιπτώσεις συνύπαρξης ΣΕΛ και ΠΣ. Σε αντίθεση με τον ήπιο φαινότυπο ΣΕΛ της δικής μας κοορτής, οι ασθενείς στη βιβλιογραφία είχαν σοβαρότερο ΣΕΛ, με τρεις ασθενείς να έχουν τουλάχιστον μια μείζονα κλινική εκδήλωση από το ΚΝΣ, τους νεφρούς ή τις αιμοποιητικές σειρες.

Συμπεράσματα

Πραγματοποιήσαμε μια αναλυτική καταγραφή των ασθενών με ΝΨΣΕΛ σε δύο ευρωπαϊκά κέντρα και συγκρίναμε την "πραγματική" αντιμετώπιση των ασθενών αυτών με τις κατευθυντήριες οδηγίες της EULAR, για να αποκαλύψουμε πιθανές αδυναμίες και «γκρίζες ζώνες» των οδηγιών. Είναι ενδιαφέρον ότι η χρονική περίοδος που μελετήσαμε περιλάμβανε κατά κύριο λόγο ΝΨ εκδηλώσεις που συνέβησαν *πριν* την έκδοση των οδηγιών το 2010. Υπό την έννοια αυτή, το συνολικά ικανοποιητικό επίπεδο συμφωνίας κλινικής πράξης-οδηγιών ανεξάρτητα από το αν η αντιμετώπιση έγινε πριν ή μετά το 2010 αποτελεί μια ενθαρρυντική παρατήρηση, δεδομένης της μακροχρόνιας διαχείρισης του ΝΨΣΕΛ στη βάση της «γνώμης του ειδικού». Παρά το γεγονός αυτό, αναγνωρίσαμε μια σειρά από «δυσαρμονίες», όπως η υπερβολική χρήση της MRI εγκεφάλου, η ανεπαρκής αξιολόγηση της γνωσιακής δυσλειτουργίας και η συχνή χρήση ανοσοκατασταλτικής θεραπείας σε περιπτώσεις ΑΕΕ, οι οποίες χρήζουν περαιτέρω εκτενέστερης έρευνας.

Σχετικά με την αποτελεσματικότητα της CYC στον ΝΨΣΕΛ, οι παρατηρήσεις μας επιβεβαιώνουν την καίρια θέση του συγκεκριμένου ανοσοκαταλτικού στην αντιμετώπιση του ΝΨΣΕΛ, αφού περισσότερο από το 80% των εκδηλώσεων εμφάνισαν τουλάχιστον μέτρια βελτίωση από την έναρξη στο τέλος της διάρκειας παρακολούθησης. Τα καλύτερα ποσοστά ανταπόκρισης στις περιπτωσεις που η CYC δόθηκε ως θεραπεία $1^{ης}$ γραμμής πιθανόν υπονοεί ότι η εντατική ανοσοκαταστολή είναι αποτελεσματικότερη αν χορηγηθεί νωρίς στην πορεία του ΝΨΣΕΛ. Παρά την αναδρομική φύση της μελέτης μας που δεν επιτρέπει την εξαγωγή ασφαλών συμπερασμάτων, οι ώσεις CYC δε θα πρέπει

να στερούνται από ασθενείς με σοβαρό ΝΨΣΕΛ, σε περιπτώσεις που η γοναδοτοξικότητα δεν αποτελεί μείζονα κίνδυνο.

Τέλος, περιπτώσεις «απομυελινωτικού συνδρόμου» δεν ανευρέθηκαν στην κοορτή μας του ΝΨΣΕΛ. Αντίθετα, με τη χρησιμοποίηση των κοορτών ΣΕΛ και ΜΣ, αναγνωρίσαμε και περιγράψαμε αναλυτικά ασθενείς με ΣΕΛ, οι οποίοι πληρούσαν παράλληλα τα διαγνωστικά κριτήρια της ΠΣ, σε συχνότητα που αντιστοιχεί σε ~ 1% των ασθενών με ΣΕΛ και αυτώ με ΠΣ. Ο συνδυασμός των παραπάνω παρατηρήσεων οδηγεί στο συμπέρασμα ότι, με δεδομένη την αυξημένη ευαισθησία των νέων διαγνωστικών κριτηρίων για την ΠΣ, η περίπτωση του « απομυελινωτικού συνδρόμου» ως ξεχωριστής οντότητας του ΝΨΣΕΛ χρήζει πιθανόν αναθεώρησης, μια και μπορεί να αναπαριστά στην πραγματικότητα αλληλεπικάλυψη δύο νοσημάτων. Οι ασθενεις με αλληλεπικάλυψη ΣΕΛ και ΠΣ στην κοορτή μας είχαν φαινότυπο ήπιου ΣΕΛ,, χωρίς μείζονες κλινικές εκδηλώσεις από τα άλλα συστήματα πλην του ΚΝΣ και δεν είχαν ανάγκη σοβαρής ανοσοκατασταλτικής θεραπείας. Αντίθετα, η ΠΣ ακολουθεί κυρίως το πρότυπο της υποτροπιάζουσας ΠΣ (relapsing-remitting MS) και συχνές υποτροπές, με μικρή ωστόσο συσσώρευση αναπηρίας· η σοβαρότητα της νευρολογικής κλινικής εικόνας υπαγόρευσε την επιλογή των ανοσοτροποποιητικών παραγόντων.

ABBREVIATIONS

aβ2GPI: Antibodies to β2GPI

aCL: Antibodies to cardiolipin

ACR: American College of Rheumatology

ACS: Acute confusional state

ACTH: Adrenocorticotropic hormone

AED: Antiepileptic drugs

AF: Auditory function

ANA: Antinuclear antibodies

aPL: Antiphospholipid antibodies

ASA: Acetylsalicylic acid

AZA: Azathioprine

BSA: Body surface area

CNS: Central nervous system

CsA: Cyclosporine A

CSF: Cerebrospinal fluid

CVD: Cerebrovascular disease

CYC: Cyclophosphamide

DIS: Dissemination in space

DIT: Dissemination in time

DWI: Diffusion-weighted imaging

EDSS: Expanded disability status scale

EEG: Electroencephalogram

EGS: EDMUS Grading Scale

EULAR: European League against Rheumatism

FLAIR: Fluid-attenuating inversion recovery sequence

GCs: Glucocorticoids

HBV: Hepatitis B virus

HCQ: Hydroxychloroquine

ICU: Intensive care unit

IQR: Interquartile range

IV: Intravenous

LA: Lupus anticoagulant

MMF: Mycophenolate mofetil

MP: Methylprednizolone

MRI: Magnetic resonance imaging

mRS: modified Rankin Scale

MS: Multiple sclerosis

MTX: Methotrexate

NCS: Nerve conduction studies

NPSLE: Neuropsychiatric SLE

PPMS: Primary progressive MS

RRMS: Relapsing remitting MS

RTX: Rituximab

SDI: SLICC/ACR Damage Index

SLE: Systemic lupus erythematosus

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

SLEDAI-2K: SLEDAI 2000 version of SLEDAI

SELENA-SLEDAI: Safety of Estrogen in Lupus Erythematosus National Assessment version of SLEDAI

SLICC: Systemic Lupus International Collaborating Clinics

SPMS: Secondary progressive MS

VA: Visual acuity

WMHIs: White matter hyperintensities

1. INTRODUCTION

1.1 Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multisystem, autoimmune connective tissue disease with a wide range of clinical manifestations. It is considered by many as the archetypal multisystem connective tissue disease[1]. The disease has a peak age of onset in young women between 18 and 40 years of age a female-to-male ratio of 9:1. This female predominance is less striking in the juvenile and elderly populations with ratios of 2–6:1 and 3–8:1, respectively, in these age groups[2]. Ethnic groups, such as those of African or Asian ancestry, are at greater risk of developing SLE and with a more severe phenotype. The incidence and prevalence of SLE seem to be increasing, probably owing to both the identification of milder cases and improved survival. In the United States population, the all race incidence was 5.1 per 100000 per year and the prevalence was 52.2 per 100000, with comparative figures of 3.8 and 26.2 in the United Kingdom, and 2.9 and 28.4 in Japan, respectively[3]. The mortality risk of SLE has decreased substantially over past decades. In a cohort of 1241 patients with lupus from a clinic in Canada, the standardized mortality ratio changed from 12.6 in the 1970s, to 3.4 in the past decade[4]. Despite the improved mortality rate, patients with systemic lupus erythematosus have a higher mortality risk than that of the general population, particularly in patients with a younger age at disease onset[5].

Lupus is a disease with protean manifestations. The frequencies with which various features of SLE are observed differ according to the stage of the disease[6, 7] (**Table 1.1**). Frequent features at disease onset are arthritis (which occurs in 52% of cases), haematological disorders (such as leukopenia in 23% of cases and thrombocytopenia in 17% of cases), malar rash (in 27% of cases), photosensitivity (in 23% of cases) and ANA positivity (in 23% of cases). At diagnosis and follow- up, the most common features are a positive ANA test result (in 88% and 96% of cases, respectively), immunological disorders (in 60% and 90% of cases), arthritis (in 55% and 71% of cases), haematological disorders (in 54% and 70% of cases), malar rash (in 38% and 62% of cases) and photosensitivity (in 34% and 52% of cases). The wide variety of neuropsychiatric manifestations will be discussed in detail below. Lupus may also cause serositis (pleurisy, pericarditis or peritonitis), gastrointestinal manifestations (abdominal pain, anorexia, nausea, vomiting, mesenteric vasculitis, lupus hepatitis), lung involvement (pneumonitis, pulmonary hemorrhage, pulmonary hypertension, pulmonary embolism) and cardiac manifestations (myocarditis, endocarditis, valvular disease, coronary artery disease). Importantly, early stages of the disease, cardinal features of SLE—such as malar rash, photosensitivity and ANA positivity—can be missing (or might be missed).

Table 1.1 Frequency of different clinical manifestations of SLE at time of diagnosis and cumulative during follow-up.

Clinical manifestation	At diagnosis (%)	Cumulative (%)
Fever	36	52
Arthralgias/arthritis	69	84
Raynaud's phenomenon	18	34
Photosensitivity	29	45
Malar rash	40	58
Discoid lupus	6	10
Oral ulcers	11	24
Serositis (Pleurisy- pericarditis)	17	36
Lymphadenopathy	7	12
Thrombocytopenia	9	22
Hemolytic anemia	4	8
Nephritis	20	30
Neuropsychiatric involvement (all manifestations)	12	27
Seizures	1	5
Psychosis	0-1	1
Cerebrovascular disease	1	5

The diagnosis of SLE is based on careful and thorough history and clinical evaluation, accompanied by abnormalities in basic laboratory investigations like complete blood count (often showing anemia, thrombocytopenia or leukopenia/lymphopenia), renal and liver function tests and acute phase reactants (erythrocyte sedimentation rate and, less commonly, C-reactive protein). Serum complement levels are reduced in patients with active SLE and are often used as surrogate biomarkers to monitor disease activity. The presence of autoantibodies is also important for the diagnosis of the disease. These include antinuclear antibodies (ANA), antibodies against double-stranded DNA (anti-ds DNA) and antibodies against extractable nuclear antigens (ENA), such as Ro (SSA), La (SSB), Sm and ribonucleoprotein (RNP).

Until recently, the diagnosis of SLE was usually based on the American College of Rheumatology (ACR) classification criteria for SLE[8, 9] (**Table 1.2**), which were developed in order to accurately diagnose the disease for the purpose of clinical research and comparison of patients from different centres. In 2012, the publication of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria was a major development in the field[10]. This classification attempted to rationalize the clinical criteria and provided a modest expansion in recognized laboratory abnormalities (**Table 1.3**). Importantly, biopsy-proven nephritis compatible with SLE in the presence of antinuclear or anti-ds DNA

Table 1.2 The revised ACR classification criteria for SLE. For the purpose of inclusion of patients in clinical studies, the diagnosis is established when ≥4 criteria are met, simultaneously or at follow-up, during any interval of observation. Modified from Hochberg MC. Arthritis Rheum 1997;40:1725.

	Criterion	Definition
1	Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2	Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3	Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4	Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5	Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6	Serositis	Pleuritis - convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion **OR** Pericarditis - documented by EKG, rub or evidence of pericardial effusion
7	Renal disorder	Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not performed **OR** Cellular casts - may be red cell, hemoglobin, granular, tubular, or mixed
8	Neurologic disorder	Seizures **OR** psychosis - in the absence of offending drugs or known metabolic derangements (uremia, ketoacidosis, or electrolyte imbalance)
9	Hematologic disorder	Hemolytic anemia - with reticulocytosis **OR** Leukopenia < than 4,000/mm^3 total on two or more occasions **OR** Lymphopenia - less than 1,500/mm3 on two or more occasions **OR** Thrombocytopenia - less than 100,000/mm3 in the absence of offending drugs
10	Immunologic disorder	Positive antiphospholipid antibody **OR** Anti-DNA - antibody to native DNA in abnormal titer **OR** Anti-Sm - presence of antibody to Sm nuclear antigen **OR** False positive serologic test for syphilis known to be positive for at least six months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11	Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

antibodies in the absence of other lupus features is regarded as sufficient for a patient to be diagnosed as having lupus. Again, the symptoms and laboratory abnormalities are cumulative and need not to be present concurrently. In the derivation set, the SLICC classification criteria resulted in fewer misclassifications than the ACR classification criteria (49 versus 70), had greater sensitivity (94% versus 86%) and comparable specificity (92% versus 93%). In the validation set, the SLICC criteria resulted in fewer misclassifications (62 versus 74), had greater sensitivity (97% versus 83%) but less specificity (84% versus 96%)[10]. The performance of the SLICC criteria have been subsequently tested in various cohorts and showed high rates of sensitivity and specificity[11-13]. Nevertheless, it is important to note that both sets of criteria have not been tested for purposes of

diagnosis. Rather, their goal is to distinguish SLE from other rheumatic diseases and strict adhesion to them in clinical practice may occasionally lead to delays in diagnosis of SLE.

Table 1.3 The 2012 SLICC classification criteria for SLE. A patient is classified as having SLE if he/she satisfies 4 of the clinical and immunologic criteria used in the SLICC classification criteria, including at least one clinical criterion and one immunologic criterion, *OR* if he/she has biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies. Modified from Petri M, *et al*. Arthritis Rheum 2012;64:2677-86.

Clinical Criteria	Immunologic criteria
1. Acute cutaneous lupus, including lupus malar rash, bullous lupus, toxic epidermal necrolysis variant of systemic lupus erythematosus, maculopapular lupus rash, photosensitive lupus rash, or subacute cutaneous lupus (psoriaform or annular polycyclic lesions, or both)	1. Antinuclear antibody concentration greater than laboratory reference range
2. Chronic cutaneous lupus, including classic discoid rash (localised and generalised), hypertrophic lupus, lupus panniculitis, mucosal lupus, lupus erythematosus tumidus, chilblains lupus, and discoid lupus/lichen planus overlap	2. Anti-ds DNA antibody concentration greater than laboratory reference range (or two-fold the reference range if tested by ELISA)
3. Oral ulcers or nasal ulcers	3. Anti-Sm: presence of antibody to Sm nuclear antigen
4. Non-scarring alopecia	4. Antiphospholipid antibody positivity as determined by any of the following: positive test result for lupus anticoagulant, false-positive test result for rapid plasma reagin, medium-titre **OR** high-titre anticardiolipin antibody concentration (IgA, IgG, or IgM), **OR** positive test result for anti-β2-glycoprotein I (IgA, IgG, or IgM)
5. Synovitis involving two or more joints and at least 30 min of morning stiffness	5. Low complement C3, low C4, low CH50
6. Serositis	6. Direct Coombs' test in the absence of haemolytic anaemia
7. Renal (urine protein-to-creatinine ratio [or 24 h urine protein]) representing 500 mg protein per 24h or red blood cell casts	
8. Neurological: seizures, psychosis, mononeuritis multiplex, myelitis, peripheral and cranial neuropathy, acute confusional state	
9. Haemolytic anaemia	
10. Leukopenia (<4000 cells per μL at least once) or lymphopenia (<1000 cells per μL at least once)	
11.Thrombocytopenia (<100000 cells/μL) at least once	

1.2 Neuropsychiatric systemic lupus erythematosus (NPSLE)

1.2.1 Definition of NPSLE, epidemiology and risk factors

SLE patients may experience a variety of neurological and psychiatric manifestations, collectively named neuropsychiatric SLE (NPSLE), that account for significant morbidity and mortality[14]. Epidemiological studies have demonstrated increasing prevalence of neuropsychiatric damage in SLE patients during the past 5 decades with a negative impact on survival[15]. Although there is considerable variation in the reported frequency of NPSLE, data from recent large cohorts suggest prevalence rates of approximately 30 – 40%[16, 17]. NPSLE is at least as common in children as it is in adults[18, 19] and in a cohort of 232 juvenile SLE in the United Kingdom followed-up over 4.5 years, pediatric BILAG-2004 score for neurologic manifestations showed involvement in 26%[20].

In 1999, the American College of Rheumatology (ACR) research committee published a set of case definitions for 19 NPSLE syndromes, in an effort to homogenize terminology for research and clinical practice purposes[21] (**Table 1.4**). These case definitions involve both the central and the peripheral nervous system, are categorized into focal and diffuse and have a wide heterogeneity that ranges from overt manifestations such as stroke, seizures and psychosis, to headache or subtle abnormalities of cognitive function. For each syndrome, diagnostic criteria and a list of alternative, non-SLE-related causes are provided. Thus, fewer than 40 – 50% of events can be ascribed to underlying lupus central nervous system (CNS) activity ("primary" NPSLE), whereas the remaining are indirectly associated to the disease and can be the consequence of metabolic disturbances, infections, or drug effects ("secondary" NPSLE)[22, 23].

Common manifestations such as headache, anxiety, mild forms of depression and cognitive dysfunction are also frequent in the general population and are usually considered to be unrelated to SLE[24, 25]. In a seminal paper published shortly after the publication of the ACR nomenclature, a population-based study showed that exclusion of such "minor" syndromes and of polyneuropathy without electrophysiological confirmation reduced NPSLE frequency by almost a half and increased the specificity of ACR nomenclature from 46 to 93%[26]. This was also illustrated in a 3-year prospective study of 370 SLE patients with a mean age of 32 years and no prior CNS manifestations. During follow-up, 76 patients (21%) reported minor CNS complaints and 16 (4.3%) developed one of the following major manifestations: seizures (2.2%), cerebrovascular disease (CVD) (1.6%), myelopathy (1.4%), optic neuritis (0.5%), aseptic meningitis (0.3%), and psychosis (0.3%)[27]. These observations have thereafter fuelled the discussion whether the aforementioned minor syndromes should actually be included in the definition of NPSLE[28, 29] and proposed attribution models tend to exclude them *a priori* from attribution to the disease (albeit an inflammatory cytokine profile has ben identified in SLE-associated intractable headache[30])(see below for attribution models of NPSLE). Among "major" neuropsychiatric manifestations, the most frequent types of NPSLE are seizure disorder, CVD, acute confusional state, psychosis, and peripheral neuropathy[17, 22, 31]. Of note,

seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, and acute confusional state have been included in the revised Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE[10].

Table 1.4 The American College of Rheumatology case definitions for NPSLE

Central nervous system		Peripheral nervous system
Focal		
Movement disorders	Cerebrovascular disease	Mononeuropathy
Myelopathy	Seizure disorder	Peripheral neuropathy
Diffuse		Cranial neuropathy
Aseptic meningitis	Demyelinating syndrome	Autonomous neuropathy
Headache	Confusion	Guillain-Barre syndrome
Psychosis	Mood disorder	Myasthenia gravis
Anxiety disorder	Cognitive dysfunction	

Identification of risk factors for NPSLE is important for providing pathogenetic insights and because their modification could be used for prevention. SLE-related factors repeatedly associated with NPSLE include generalized (non-neurological) SLE activity or damage, history of previous or concurrent other major NPSLE, and antiphospholipid (aPL) antibodies [persistently positive moderate-to-high anti-cardiolipin (aCL) or anti-β2 GPI IgG/IgM titers or the lupus anticoagulant (LAC)][32, 33]. In the SLICC inception cohort of more than 1000 SLE patients assessed prospectively for up to 10 years, presence of LAC at baseline was associated with subsequent intracranial thrombosis, whereas antiribosomal P antibody was a risk factor for SLE-related psychosis[34, 35]. Higher non-neurological damage and disease activity conferred risk for seizures[36]. In a cross-sectional study of 959 SLE patients, aPL antibodies and/or antiphospholipid syndrome (APS) was the strongest risk factor for primary NPSLE, particularly focal neuropsychiatric events[37]; disease activity and damage also showed association, whereas anti-Ro/ SSA antibodies were inversely associated. Other studies have demonstrated relationship between increased SLE disease activity or damage and diffuse or CNS neuropsychiatric events[38], as well as with specific manifestations such as peripheral neuropathy[39] and cognitive dysfunction[40]. Factors not specific to SLE such as increasing age, hypertension, and other atherosclerotic risk factors, have been associated with cognitive dysfunction, depression, and CVD[37, 41-43]. Although these associations are subject to confounding bias and cannot ascertain causal inferences, they suggest a role for disease-driven inflammation and aPL antibody-mediated vasculopathy in NPSLE[44]. Importantly, evaluation for these risk factors, together with information about the timing and type of manifestations and the results from

neuroimaging and other laboratory studies, can be helpful in attribution of neuropsychiatric events to SLE (**Table 1.5**).

Table 1.5 Suggested approach to attributing a neuropsychiatric event to SLE

Exclusion of secondary causes	Exclusion of infection, hormonal/metabolic disturbances, vitamin deficiencies, drug effects, and association factors reported in the ACR nomenclature and case definitions for NPSLE [21, 33, 45]
Type of event: minor versus major	Minor NP events (headache, anxiety, mild forms of depression and cognitive dysfunction, polyneuropathy without electrophysiological confirmation) are less likely to be attributed to SLE (specificity 46% versus 93% for major NP events) [26]
Timing of event	Most (50–60%) SLE-related events occur at disease onset or within the first 1-2 years after diagnosis; events occurring >6 months before the onset of SLE are less likely to be attributed to SLE [33, 45, 46]
Assessment for risk factors for SLE-related event	Major risk factors for SLE-related events include generalized (non-neurological) SLE activity or damage, history of previous or concurrent other major NPSLE, aPL antibodies (persistently positive moderate-to-high aCL or anti-β2 GPI Ig titers, LAC) [33, 34, 45, 46]
Assessment for risk factors for SLE-unrelated event	Risk factors for SLE-unrelated events include increasing age, atherosclerotic risk factors (hypertension, diabetes, dyslipidemia), heart valvular disease, chronic atrial fibrillation, high cumulative dose of glucocorticoids (>10 g) [33, 45]
Results from neuroimaging studies	MRI abnormalities (small punctuate hyperintense T2-weighted focal lesions in subcortical and periventricular WM, diffuse cortical GM lesions, cerebral atrophy, infarcts) especially when multiple in number and bihemispheric, and in the absence of confounding factors (increased age, atherosclerotic risk factors, heart valvular disease, long-standing lupus) have increased specificity (>70–80%) for primary NPSLE [32, 33]
Results from other laboratory studies	CSF abnormalities (pleocytosis, increased protein, low glucose) in the absence of CNS infection are found in 30–40% of active primary NPSLE [32, 33] EEG activity (spike-wave or unspecific slowing activity) in the absence of brain structural abnormalities has 50–60% sensitivity and specificity for active primary NPSLE; in seizure disorder, epileptiform activity predictive for seizure recurrence (PPV 73%, NPV 79%) [32, 33]
Clinical response to treatment	Clinical response to anti-inflammatory or antiplatelet/anticoagulation treatment favors the attribution to SLE [45]

1.2.2 Attribution models for NPSLE: The SLICC models and the Ferrara algorithm

As already mentioned, the issue of attribution of neuropsychiatric events to the disease *per se* (ie. "primary" NPSLE), rather than to comorbidities or complications of therapy, still remains a challenging issue, owing to the wide heterogeneity of manifestations and a dearth of specific diagnostic tests. Ultimately, the "gold standard" continues to be the clinical judgment of an experienced physician, often following a multidisciplinary approach, which involves various medical specialties.

To facilitate the decision of attributing a neuropsychiatric manifestation to SLE, different attribution models have been proposed. These take into account various parameters, including type of neuropsychiatric manifestation ("major" vs. "minor"), timing of neuropsychiatric event relative to SLE diagnosis (before, after or concomitant with the diagnosis of SLE) and presence of concurrent factors, either in favor of or against attribution to SLE. In particular, the SLICC inception cohort has created two models of different stringency[47, 48]. In model A (the most stringent), only neuropsychiatric events in which the onset occur within the enrollment window (6 moths prior until15 months after the diagnosis of SLE), have no exclusion or association factors present (as defined by the ACR definitions) and are not one of the "minor" events identified by Ainiala *et al*[26] are attributed to SLE. In the more lenient model B, additional neuropsychiatric events in which the onset occurred within 10 years prior to SLE diagnosis and were still present within the enrollment window and had no exclusion factors (presence of "association" factors is eligible) were also attributed to SLE. It should be noted that the investigators do not compare model-based attribution with physician judgment, rather the former is used as a rule[47, 48]. Also, as the SLICC cohort is an inception cohort studying SLE patients at or close to the time of disease diagnosis, neuropsychiatric manifestations that may occur years after diagnosis are inevitably excluded by the SLICC attribution models.

More recently, the Italian Study group on NPSLE published an attribution algorithm leading to a probability score for a specific manifestation to be attributed to SLE (**Table 1.6**)[49]. This model takes into account the aforementioned parameters of the SLICC models (timing, type of event and presence of confounding factors), adding also the presence or not of "favouring" factors for attributing an event to SLE (based on a systematic literature review and expert opinion). Each of these items is scored as shown in table 2.3 and the resulting sum of all scores has a value of 0-10. The authors compared the model against physician judgment in two separate cohorts of NPSLE patients (a training and a validating cohort) and found that a cut-off score of ≥ 6 was associated with 83% sensitivity and 70% specificity, when physician judgment was used as the "gold standard". Increasing the total score to > 7 showed an estimated probability of being SLE-related, of 100% and 86% in the training and validating cohorts, respectively.

Table 1.6 Categorization and weighting of the selected items incorporated into the Ferrara algorithm. Modified from Bortoluzzi A, *et al.* Rheumatology (Oxford). 2014 (epub ahead of print)

Item 1. Time of the onset of NP event with respect to SLE clinical onset	
Before (>6 months before SLE onset)	**0**
Concomitant (within 6 months of SLE onset)	**3**
After (>6 months after SLE onset)	**2**
Item 2. Minor or not specific NP events as defined by Ainiala *et al* [26] [a]	
Present (i.e. minor or common NP events as proposed by Ainiala *et al* [26]) [a]	**0**
Absent (i.e. NP events other than those proposed by Ainiala *et al* [26]) [a]	**3**
Item 3[b]. Confounding factors or not SLE-related associations as defined by the ACR glossary	
None or not applicable	**2**
Present (one confounding factor)	**1**
Present (more than one confounding factor)	**0**
Item 4[b]. Additional (or favouring) factors	
None or not applicable	**0**
Present (one additional or favouring factor)	**1**
Present (more than one additional or favouring factor)	**2**

[a] List of NP pictures deemed as minor or common known to occur frequently in normal healthy population controls: headaches, anxiety, mild depression (mood disorders failing to meet the criteria for major depressive-like episodes), mild cognitive impairment (deficit in fewer than three of the eight specified cognitive domains) and polyneuropathy without electrophysiological confirmation

[b] A list of confounding and favouring factors is given in supplementary Tables of the original manuscript at Rheumatology Online. NP: neuropsychiatric.

1.2.3 Pathogenesis of NPSLE

The pathogenesis of NPSLE involves autoantibody-mediated neuronal or vascular injury, intrathecal production of inflammatory cytokines, disruption of the blood-brain barrier (BBB), and accelerated atherosclerosis[32]. Driven by initial observations in paraneoplastic syndromes, there is increasing appreciation of the role of brain-reactive autoantibodies in the pathogenesis of various neuropsychiatric syndromes[50]. In this regard, an increasing number of autoantibodies, both systemic and brain-specific, have been associated with SLE[35, 51]. Diamond and colleagues have shown that a subset of anti-DNA antibodies can cross-react with both murine and human NR2 subunits of the N-methyl-D-aspartate receptors (NMDAR) and induce neuronal apoptotic cell death[52]. NR2 receptors are abundant in the hippocampus, a brain region implicated in learning and memory processes, and circulating murine and human anti-NR2 antibodies may induce hippocampal apoptosis and cognitive dysfunction in mice in the presence of breached BBB[53, 54]. At low concentration, anti-NR2 antibodies augment NMDAR-mediated excitatory postsynaptic potentials, whereas at high concentration, they

cause excitotoxicity through enhanced mitochondrial permeability transition[55]. Another group showed that incubation of human umbilical vein endothelial cells with purified anti-NR2/anti-DNA antibodies from SLE sera upregulated the expression of surface adhesion molecules and the production of IL-6 and IL-8[56]. If confirmed, these results suggest a mechanism by which peripherally produced anti-NR2 antibodies can lead to inflammation and BBB disruption, therefore gaining access to the CNS to initiate NPSLE. Anti-NR2 antibodies are present in the serum or cerebrospinal fluid of 30–40% of SLE patients, and an association with NPSLE – especially cognitive dysfunction and mood disorders – has been reported in some but not all studies[34, 57].

Anti-ribosomal P antibodies, which target the neuronal surface P antigen (NSPA), cause robust apoptotic cell death due to increased calcium influx[58] and are considered highly specific for NPSLE[59]. Two recent elegant studies from the same group showed that NSPA is involved in glutamatergic transmission related to memory in the hippocampus and that injection of anti-ribosomal P antibodies from the sera of NPSLE patients are able to impair memory in mice via neuronal apoptotic death or functional perturbations[60, 61]. Interestingly, as with anti-NR2, anti-ribosomal P antibodies have also been associated with neurocognitive impairment in SLE patients[62]. Further standardization and validation will be required to determine the clinical utility of these antibodies.

Recently, the 16/6 idiotype antibody, a human anti-single-stranded-DNA antibody originated from a patient with cold agglutinin disease, was shown to hamper visual recognition and spatial memory in intracerebra-ventricularly injected C3H female mice[63]. Immunohistochemistry analysis revealed an increase in astrocytes and microglial activation in the hippocampus and amygdala in the autoantibody-injected group[63]. Although the relevance of these antibodies in human NPSLE is yet unknown, these findings suggest that brain-reactive autoantibodies with different specificities and at different concentrations might contribute to pathogenesis of diverse NP syndromes in SLE[64].

1.2.4 The role of brain imaging in NPSLE

Conventional MRI remains the ‘gold standard’ in NPSLE imaging due to its wide availability and capability to identify CNS lesions. However, MRI carries significant limitations in terms of sensitivity and specificity not least due to the heterogeneity of NPSLE *per se*. A recent inventory of cerebral abnormalities seen on MRI confirmed that the most frequent pattern in SLE is that of small punctate hyperintense T2-weighted focal lesions in subcortical and periventricular white matter, usually with no contrast enhancement (white matter hyperintensities, WMHIs)[65]. The precise role of these lesions in NPSLE remains elusive, as similar foci can be found in patients without neuropsychiatric manifestations and in the general population after mid-adult life[66]. Interestingly, a recent study using follow-up MRI after 20 years of baseline showed increase in number and volume of such WMHIs over time and an independent association with new neuropsychiatric manifestations[67]. Concomitant restricted diffusion of such MRI lesions suggests cytotoxic edema due

to focal ischemia but whether this represents frank vasculitis or noninflammatory thrombotic vasculopathy has not been elucidated. Notably, in a subset of NPSLE patients (12%), MRI shows diffuse, cortical lesions in the grey matter, similar to the lesions that develop following seizures[65, 68]. This underrecognized finding is pathophysiologically distinct from white matter lesions and could represent immune response against neuronal components; nevertheless, a clear association between any specific MRI finding and autoantibody-mediated CNS damage is lacking.

More than 40% of SLE patients with various neuropsychiatric manifestations show normal MRI scans[23, 65, 69]. For these patients, more advanced imaging techniques have been elaborated to detect subtle aberrations in brain structure or cerebral blood flow[70]. Magnetization transfer imaging, diffusion- weighted MRI, magnetic resonance spectroscopy, functional MRI, perfusion-weighted imaging, have all been applied in NPSLE. These modalities have uncovered abnormalities in the otherwise 'normal- appearing' brain regions in SLE patients with or even without neuropsychiatric manifestations, such as regional grey matter atrophy[71], increased cerebral blood flow[72], and abnormal patterns of brain activation during neurocognitive assessment[73].

Brain positron emission tomography (PET), which measures metabolic activity by 2 – 18F-fluoro-2-deoxyglucose (FDG) uptake, has also been employed in NPSLE. Hypermetabolism is thought to reflect active inflammation, whereas decreased FDG uptake is a marker of impending tissue loss and atrophy. The most prevalent finding in active NPSLE is grey matter hypometabolism in the frontal, parietal, or occipital lobe[74]. By contrast, a recent cross-sectional study revealed hypermetabolism in the hippocampus and orbitofrontal cortex that correlated with impaired memory performance and mood alterations in SLE patients[75]. PET can identify fluctuations in regional cerebral metabolism even in the absence of MRI lesions[76, 77]. In a cohort of SLE patients without neuropsychiatric manifestations, PET confirmed grey matter hypometabolism and revealed increased FDG uptake in heavily myelinated white matter tracts correlating with generalized disease activity[78]. This could represent ongoing CNS inflammation early in the course of the disease, and the authors proposed that grey matter disorder (apoptosis/atrophy) might represent a late stage sequel of remote white matter inflammation through a mechanism of diaschisis on areas where these nerve fibers project[78]. Together, and notwithstanding advances in neuroimaging, progress in our understanding of the mechanisms underlying NPSLE has been rather modest, and the diagnostic utility of such techniques remains at present investigational.

1.2.5 Treatment options in NPSLE

Treatment of NPSLE is plagued by paucity of controlled trials and current therapeutic approaches remain at large empirical. Corticosteroids, immunosuppressants, antiplatelet/anticoagulant treatment and symptomatic drugs are used depending on the presumptive pathogenic mechanism[32, 33]. Immunosuppressive treatment (corticosteroids alone or with immunosuppressants such as

azathioprine or cyclophosphamide) is generally indicated for manifestations that are felt to reflect an immune/ inflammatory state (acute confusional state, aseptic meningitis, myelitis, cranial, and peripheral neuropathies and psychosis), following exclusion of non- SLE-related causes. When manifestations indicate a thrombotic state, particularly CVD especially in the presence of aPL antibodies or APS, antiplatelet or anticoagulation treatment is used[33]. However, as shown in the results of our study, clinical practice shows that these two states are not always possible to differentiate or they may coexist.

Aside from use of immunosuppression in few selected cases, the management of SLE CVD should be similar to the one in patients without SLE. Consultation with a stroke specialist is necessary to identify candidate patients for thrombolysis or other specialized management options. For patients who are not candidate for acute thrombolysis, updated international recommendations consider aspirin as the mainstay for secondary prevention, over clopidogrel, or anticoagulants[79]. In patients with persistently positive, moderate-to-high titers of aPL antibodies, optimal treatment remains a matter of debate, with both advocates of high intensity anticoagulation (target INR >3.0) and supporters of lower intensity or sole antiplatelet treatment[80].

In lupus myelopathy, often associated with aPL antibodies [81], a systematic review concluded that anticoagulation provided no additional benefit over standard immunosuppression[82]. On the contrary, intensive immunosuppression is of paramount importance and a recent report suggests that rituximab may prove a valuable option[83]. B-cell depletion has been used in the treatment of NPSLE, including cases refractory to conventional immunosuppression. Although data come from uncontrolled studies, results are encouraging with more than 80% of patients showing at least partial clinical response[84, 85].

Symptomatic treatment in NPSLE includes anticonvulsants for seizures, antidepressants for mood disorder or antipsychotics medications for psychosis. The role of pharmacologic treatment in cognitive dysfunction remains uncertain, and a controlled study [86] of memantine – a serotoninergic receptor and nicotine acetylcholine receptor antagonist used in Alzheimer's disease – found no significant improvement in cognitive performance against placebo in SLE patients.

NPSLE has been associated with refractory disease, increased organ damage and disease costs, as well as with lower health-related quality of life[22, 87-89]. Major events such as CVD, severe cognitive dysfunction, myelopathy, and optic neuritis often result in significant morbidity and poor functional outcomes[32]. Nevertheless, prompt initiation of immunosuppressive and symptomatic treatment can result in improved long-term outcomes, at least for certain manifestations such as psychosis[88, 90] and peripheral neuropathy[39]. Data regarding the impact of NPSLE on survival are scarce and conflicting, ranging from no increased mortality[91, 92] to highly increased mortality rates without improvement of survival over the past decades [15, 93, 94]. A recent retrospective study calculated a standardized mortality ratio of 9.5 compared to the general population, with infections and NPSLE *per se* being the main causes of death [95].

1.2.6 EULAR recommendations for diagnosis and management of NPSLE

Notwithstanding the significant advances in our understanding of its pathogenesis, NPSLE continues to pose considerable diagnostic and therapeutic challenges. Diagnostic workup and treatment decisions are typically performed on a patient-by-patient basis and often necessitate the involvement of multiple medical specialties. In an effort to homogenize the management of patients with NPSLE, a European League Against Rheumatism (EULAR) task force issued a set of recommendations in 2010, addressing diagnostic and therapeutic issues using an evidence-based approach followed by expert consensus (average agreement among experts: 9.1/10)[33]. The recommendations cover both general NPSLE and specific NPSLE disorders, identify risk factors for its occurrence, and provide evidence.

The EULAR recommendations comprise a total of 27 statements addressing both the general approach to NPSLE and individual neuropsychiatric syndrome on the value of diagnostic modalities and therapeutic options. The guidelines fulfilled all 23 items of the Appraisal of Guidelines Research and Evaluation (AGREE) instrument and are shown in **Table 1.7**.

Figure 1.7 The EULAR recommendations for the diagnosis and management of NPSLE. Adapted from Bertsias G, *et al*. Ann Rheum Dis 2010; 69: 2074-82

General NPSLE
Neuropsychiatric events may precede, coincide, or follow the diagnosis of SLE but commonly (50–60%) occur within the first year after SLE diagnosis, in the presence of generalis disease activity (40–50%)
Cumulative incidence
Common (5–15% cumulative incidence) manifestations include CVD and seizures; Relatively uncommon (1–5%): severe cognitive dysfunction, major depression, ACS and peripheral nervous disorders; Rare (<1%) are psychosis, myelitis, chorea, cranial neuropathies and aseptic meningitis.
Risk factors
Strong (fivefold increase) risk factors consistently associated with primary NPSLE are generalised SLE activity, previous severe NPSLE manifestations (especially for cognitive dysfunction and seizures), and antiphospholipid antibodies (especially for CVD, seizures, chorea)
Diagnostic work-up
In SLE patients with new or unexplained symptoms or signs suggestive of neuropsychiatric disease, initial diagnostic work-up should be similar to that in non-SLE patients presenting with the same manifestations Depending upon the type of neuropsychiatric manifestation, this may include lumbar puncture and CSF analysis (primarily to exclude CNS infection), EEG, neuropsychological assessment of cognitive function, NCS, and neuroimaging (MRI) to assess brain structure and function
The recommended MRI protocol (brain and spinal cord) includes conventional MRI sequences (T1/T2, FLAIR), DWI, and gadolinium-enhanced T1 sequences
Therapy
Glucocorticoids and immunosuppressive therapy are indicated for neuropsychiatric manifestations felt to reflect an immune/ inflammatory process (eg, ACS, aseptic meningi myelitis, cranial and peripheral neuropathies and psychosis) following exclusions of non-SLE-related causes
Antiplatelet/anticoagulation therapy is indicated when manifestations are related to antiphospholipid antibodies, particularly in thrombotic CVD
The use of symptomatic therapies (eg, anticonvulsants, antidepressants) and the treatment of aggravating factors (eg, infection, hypertension and metabolic abnormalities) should a be considered
Antiplatelet agents may be considered for primary prevention in SLE patients with persistently positive, moderate or high, antiphospholipid antibody titres
Specific NPSLE disorders

CVD
Atherosclerotic/thrombotic/embolic CVD is common, haemorrhagic stroke is rare, and stroke caused by vasculitis is very rare in SLE patients; accordingly, immunosuppress therapy is rarely indicated
Long-term anticoagulation should be considered in patients with stroke who fulfil the classification criteria for antiphospholipid syndrome for secondary prevention of recurrent stroke which commonly occurs
Cognitive dysfunction
Mild or moderate cognitive dysfunction is common in SLE but severe cognitive impairment resulting in functional compromise is relatively uncommon and should be confirmed by neuropsychological tests in collaboration with a clinical neuropsychologist when available
Management of both SLE and non-SLE-associated factors as well as psycho-educational support may prevent further deterioration of cognitive dysfunction; progressive cognitive decline develops only in a minority of patients
Seizure disorder
Single seizures are common in SLE patients and have been related to disease activity. Chance of recurrence is comparable to that in the general population
The diagnostic work-up aims to exclude structural brain disease and inflammatory or metabolic conditions and includes MRI and EEG
In the absence of MRI lesions related to seizures and definite epileptic abnormalities on EEG following recovery from the seizure, withholding of AED after a single seizure should be considered. Long-term anti-epileptic therapy may be considered for recurrent seizures
For most patients without generalised disease activity, immunosuppressive therapy is not indicated for prevention of recurrences or control of refractory seizures
Anticoagulation may be considered in patients with antiphospholipid antibodies
Movement disorders (chorea)
In addition to symptomatic therapy for persistent symptoms (dopamine antagonists), antiplatelet agents may be considered in SLE patients with antiphospholipid antibodies
Glucocorticoids/immunosuppressive and/or anticoagulation therapy may be considered in severe cases when generalised disease activity and/or thrombotic manifestations are present
ACS

Lumbar puncture for CSF analysis and MRI should be considered to exclude non-SLE causes, especially infection
Glucocorticoids and immunosuppressive therapy may be considered in severe cases
Major depression and psychosis
Major depression attributed to SLE alone is relatively uncommon while psychosis is rare; although steroid-induced psychosis may occur this is very rare
There is no strong evidence to support the diagnostic utility of serological markers or brain imaging in major depression
Glucocorticoids and immunosuppressive therapy may be considered in SLE-associated psychosis, especially in presence of generalised disease activity
Myelopathy
The diagnostic work-up includes gadolinium-enhanced MRI and cerebrospinal fluid analysis
Timely (as soon as possible) induction therapy with high-dose glucocorticoids followed by intravenous cyclophosphamide should be instituted
Maintenance therapy with less intensive immunosuppression to prevent recurrence may be considered
Optic neuritis is commonly bilateral in SLE
The diagnostic work-up should include a complete ophthalmological evaluation (including funduscopy and fluoroangiography), MRI and visual evoked potentials
Optic neuritis needs to be distinguished from ischaemic optic neuropathy, which is usually unilateral, especially in patients with antiphospholipid antibodies
Glucocorticoids (intravenous methylprednisolone) alone or in combination with immunosuppressive agents should be considered, but failures are common
Peripheral neuropathy
Peripheral neuropathy often co-exists with other neuropsychiatric manifestations and is diagnosed with electromyography and NCS
Combination therapy with glucocorticoids and immunosuppressive agents may be considered in severe cases

ACS, acute confusional state; AED, anti-epilectic drug; CNS, central nervous system; CSF, cerebrospinal fluid; CVD, cerebrovascular disease; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuating inversion recovery sequence; NCS, nerve conduction studies; NPSLE, neuropsychiatric systemic lupus erythematosus; SLE, systemic lupus erythematosus.

1.3 Demyelination in SLE: NPSLE or multiple sclerosis

1.3.1 Multiple sclerosis (MS)

The term 'demyelination' describes a loss of the lipid-rich myelin sheaths with relative preservation of axons. Multiple sclerosis (MS) is a chronic inflammatory disease characterized by multifocal areas of demyelination in the white matter (WM) of the brain and the spinal cord. Its diagnosis necessitates objective evidence of central neurological dysfunction indicative of 'dissemination in space and time' (more than one affected area and more than one episode), provided that other possible explanations have been excluded[96]. Traditionally, diagnosis of MS necessitates dissemination of symptoms in space (DIS) and time (DIT), which could take months or years before being established with certainty. To improve sensitivity and allow for earlier MS diagnosis, especially in the case of a clinically isolated syndrome (ie. a first clinical episode of acute or subacute onset, with symptoms and signs suggestive of an inflammatory demyelinating disorder of the CNS, by definition lasting for at least 24 h), the 2010 revision of the McDonald criteria simplified interpretation of MRI, so that DIS and DIT can be established from a single brain MRI scan[97].

1.3.2 "MS-like" syndromes in SLE

NPSLE, on the other hand, can occasionally present with a clinical picture resembling MS. In the past, the term "lupoid sclerosis" was coined to describe SLE patients with complex neurologic deficits similar to those seen in MS [98]. However, its vague definition was a source of confusion and hence it has now practically been abandoned. The ACR nomenclature has instead introduced the term "demyelinating syndrome", with diagnostic criteria resembling those of definite MS which include symptomatic CNS WM lesions, transverse myelopathy, optic neuropathy, diplopia due to nerve palsies or internuclear ophthalmoplegia and brain stem disease, each occurring at a different time point (**Table 1.8**)[21]. It is noteworthy that transverse myelopathy and optic neuropathy are also listed as separate case definitions, since they can occur as isolated entities. Patients who meet criteria for these and for demyelinating syndrome should be classified as having both.

Table 1.8 Definition of demyelinating syndrome according with the ACR nomenclature and case definitions for NPSLE syndromes

Demyelinating syndrome Acute of relapsing demyelinating encephalomyelitis with evidence of discrete neurologic lesions distributed in place and time	
To fulfill the criteria for this definition two or more of the following, each occurring at different times, or one of the following occurring on at least two different occasions must be present	1. Multiple discrete areas of damage to white matter within CNS, causing one or more limbs to become weak with sensory loss
	2. Transverse myelopathy
	3. Optic neuropathy
	4. Diplopia due to isolated nerve palsies or internuclear ophthalmoplegia
	5. Brainstem disease with vertigo, vomiting, ataxia, dysarthria or dysphagia
	6. Other cranial nerve palsies

In routine clinical practice, patients often present with an isolated neurological syndrome, which poses a big diagnostic problem because it may be the first clinical episode of multiple sclerosis (MS) or the only manifestation of systemic lupus erythematosus (SLE) before other typical features of the disease appear[99, 100]. Indeed, the immunological nature of both MS and SLE, the shared epidemiological characteristics of the affected populations, similar neurological manifestations caused by the demyelinating syndrome, the relapsing–remitting course and the presence of multifocal WM lesions on brain MRI often complicate the differentiation of the two conditions at the time of presentation, and in many cases the diagnosis can only be made after a long-term follow-up[101, 102].

To avoid MS misdiagnosis, Miller *et al* have suggested a series of paraclinical findings (red flags) that might signal a more likely alternative diagnosis than MS[100]. Thus, in a patient presenting with CNS plus one of the considered major/intermediate red flags (renal involvement, livedo reticularis, rash, arthritis, arthralgias, myalgias, headache, meningismus or neuropsychiatric syndrome), the diagnosis of SLE should be strongly considered, even if no other criteria are present. Other manifestations such as cerebrovascular disease would suggest concomitant antiphospholipid syndrome (APS) in the presence or absence of SLE. Moreover, cerebral venous sinus thrombosis, livedo reticularis and recurrent spontaneous abortions or thrombotic events are major red flags that obligate us to exclude APS with or without SLE. Indeed, APS may present with a wide variety of neurologic manifestations beyond stroke[103]. In an early study, Cuadrado *et al* examined 27 patients initially labeled as "possible MS" with atypical features (atypical imaging findings or evolution, symptoms suggestive of connective tissue disease), referred to a lupus clinic; all patients tested

positive for aPL and actually fulfilled criteria for APS (either primary or secondary)[104]. Notwithstanding the limitation of potential referral bias, this observation led some experts to include APS in the differential diagnosis of MS, especially when the latter presents with atypical findings[105].

By using the ACR definition of demyelinating syndrome, the latter is considered a rare manifestation of NPSLE (cumulative incidence ~ 0.3% of SLE patients)[17, 32]. Recent cohorts of NPSLE patients from different countries have confirmed very low prevalence rates, ranging from 0-1.9% of all NPSLE manifestations[22, 23, 37, 69].

2. RESEARCH QUESTIONS AND AIM OF THE STUDY

NPSLE poses a diagnostic and therapeutic challenge. Attribution of neuropsychiatric events to lupus warrants a thorough investigation and exclusion of alternative causes. Diagnostic workup and treatment decisions are typically performed on a patient-by-patient basis and often necessitate the involvement of multiple medical specialties. In an effort to homogenize the management of patients with NPSLE, a EULAR task force has issued a set of recommendations addressing diagnostic and therapeutic issues, using a combination of evidence-based approach and expert consensus. A validation or comparison of these recommendations with routine clinical practice has not been performed.

Distinction of SLE-related demyelinating syndrome from frank multiple sclerosis (MS) is not clear, given the recent advances in MS diagnostics, which aim to increase sensitivity in diagnosing the disease.

For the purpose of this Thesis, we performed a comprehensive study of NPSLE in two European centres (with the cooperation of a EULAR scholar, Dr. Cristina Pamfil from «Iuliu Hatieganu» University of Pharmacy and Medicine, Cluj-Napoca, Romania). More specifically we:

- analyzed demographic, clinical and neuroimaging data from all «primary» NPSLE cases from Heraklion and Cluj
- compared routine clinical practice against the EULAR recommendations for NPSLE to unveil potential pitfalls and limitations
- evaluated treatment options and long-term outcome of NPSLE - analyzed in more detail patients that received cyclophosphamide (CYC) for severe neuropsychiatric manifestations, using a structured approach to assess response
- identified SLE patients with clinical and neuroradiological features of demyelination and classified them as SLE-associated demyelinating syndrome or coexistence of SLE with frank MS, by diagnostic criteria.

3. PATIENTS AND METHODS

3.1 Characterization of the NPSLE cohort and comparison of usual clinical care with the EULAR recommendations: Two national tertiary referral centres for patients with SLE and suspected neuropsychiatric involvement, Heraklion, Greece and Cluj, Romania participated in the study. Patients with confirmed neuropsychiatric involvement were selected by retrospective chart review from 650 lupus cases over the period 2001-2012. All patients fulfilled at least four of the revised ACR classification criteria for SLE[9] at the time of NPSLE diagnosis and had undergone regular follow-up in each centre.

For each neuropsychiatric manifestation included in our study, we recorded all diagnostic procedures the patients underwent and the therapies they received. The following variables were also documented: age, gender, ethnicity, smoking and cardiovascular risk factors, disease duration, presence of aPL, history of previous major organ involvement and medication history. Disease activity and damage were cross-sectionally assessed at the time of neuropsychiatric event with the Safety of Estrogen in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) [106] and the SLICC/ACR Damage Index (SDI), respectively[107, 108]. Time lag between diagnosis of SLE and occurrence of NPSLE was calculated in years.

Presence of generalized disease activity at the time of neuropsychiatric event was defined as:

i) a SELENA-SLEDAI ≥ 4, after exclusion of the neuropsychiatric components (non-neuropsychiatric SELENA-SLEDAI). Although not a formally validated index for disease activity, we used the non-neuropsychiatric SELENA-SLEDAI to capture extra-neuropsychiatric disease activity. The cut-off value of ≥ 4 was chosen based on data showing that total SLEDAI (SLEDAI-2K version) scores above 3 or 4 may be more appropriate to define active disease associated with intensification of immunosuppressive therapy [109].

ii) in case of non-neuropsychiatric SELENA-SLEDAI < 4, if the physician global assessment of disease status (PGA), as incorporated in the SELENA-SLEDAI form, was ≥ 2, indicative of at least medium disease activity [106]. This cut-off value of PGA has been used in previous observational studies to denote severe disease in SLE [110].

Neuropsychiatric events, work-up and outcome: Neuropsychiatric events were defined according to the ACR nomenclature and case definitions [21]. For patients experiencing more than one neuropsychiatric event, each event was registered individually. The attribution of neuropsychiatric syndromes to SLE was based on physician judgment and was made by the treating physician with the help of experts from different disciplines including: internal medicine, infectious diseases, neurology, psychiatry, and neuroimaging. Attribution to SLE followed fulfilment of the following criteria: (1) diagnosis of SLE (ACR criteria); (2) presence of neuropsychiatric manifestation included in the ACR nomenclature for NPSLE; (3) absence of another diagnosis that could potentially explain

symptoms, according to the "exclusion" and "association" factors of the ACR nomenclature [21]; alternative diagnoses included, but were not limited to, central nervous system (CNS) infections, metabolic abnormalities, and adverse drug reactions. Following their exclusion, only events directly attributed to lupus were included in the study.

The standard neuroimaging procedure for NPSLE in both centres is the EULAR-recommended brain/spinal cord magnetic resonance imaging (MRI) protocol which includes conventional MRI sequences (T1/T2, FLAIR), diffusion-weighted imaging (DWI), and gadolinium-enhanced T1 sequence. Brain MRIs were interpreted by confirmed neuroradiologists in each centre (both referral centres for NPSLE), as part of the standard approach to diagnosing possible NPSLE. Abnormalities including white and grey matter hyperintensities, cerebral infarcts, intracranial haemorrhages, cerebral venous thromboses and brain atrophy, were recorded. MRI results were classified as either "diagnosis specific" when findings were diagnostic of a specific neuropsychiatric entity, or "diagnosis non-specific/useful for exclusion of other causes" in all other cases.

Due to the heterogeneity of manifestations, outcome of neuropsychiatric events was evaluated at six months according to an arbitrary 3-level categorical outcome: «improved», «stable» or «worsened».

Comparison of clinical care with the EULAR statements and recommendations: The EULAR recommendations comprise a total of 27 statements addressing both the general approach to NPSLE and individual neuropsychiatric syndromes [33]. To calculate concordance rates between clinical practice and the recommendations, we extracted these 27 statements and scrutinized the manuscript text for additional recommendations not included in the statements. Next, we compared the diagnostic and therapeutic decisions applied in each registered neuropsychiatric event against the EULAR recommendations (both the general ones and those specific to the event). In calculation of concordance rates we excluded cases of lupus headache, autonomic disorder and anxiety disorder, since the optimal work-up and treatment for these manifestations is not discussed in the recommendations.

Since the EULAR recommendations were published in 2010, our study period largely reflected usual care prior to their publication. To assess their potential impact on the management of NPSLE, we performed a post-hoc analysis to compare agreement between usual care and recommendations relative to the time period of NPSLE occurrence (prior to versus after 2010).

Statistical analysis: Data analyses were performed with IBM SPSS Statistics (version 21.0). Descriptive statistics were undertaken for continuous variables and median values/interquartile ranges (IQR) were calculated. Chi-square or Fisher's exact test were used to compare categorical variables and the non-parametric Mann-Whitney U test was used to compare continuous variables. Statistical significance was indicated as a two-sided $p<0.05$.

3.2 Efficacy and safety of CYC for NPSLE: To assess the efficacy and safety profile of CYC in NPSLE, we included "primary" NPSLE cases who received CYC: i) specifically for their

neuropsychiatric syndrome, either as first-line induction therapy or as "rescue" therapy in disease refractory to previous immunosuppressants, and ii) due to coexisting non-neuropsychiatric major disease manifestation (eg. severe renal or hematologic disease) but had a concomitant active neuropsychiatric manifestation attributed to SLE. The following variables were documented: i) route and dosing scheme of CYC administration, ii) cumulative CYC dose and total number of intravenous (IV) pulses, in case of IV administration, iii) accessory IV methylprednisolone (MP) pulses in the beginning of CYC therapy and cumulative MP dose, iv) type of maintenance or "rescue" therapy, in case response to CYC treatment was satisfactory or suboptimal, respectively, v) duration of follow-up from last CYC dose to most recent visit, vi) outcome of neuropsychiatric manifestation at most recent visit, vii) relapses of initial manifestation, either while on CYC or during maintenance therapy, and time-to-relapse, viii) major side-effects during follow-up, with particular interest in neoplasias, severe infections and gonadal toxicity and ix) application or not of gonadal protection during CYC therapy with monthly gonadotropin releasing hormone (GnRH) agonists.

Outcome measures: Due to the heterogeneity of neuropsychiatric clinical syndromes, we used a generic physician judgment-based 4-point Likert scale, as follows: 1: Complete response (CR, complete resolution of initial symptoms/ neurological signs); 2: Partial response (PR, improvement but without disappearance of initial symptoms/signs); 3: Stabilization (absence of clinically significant change in symptoms/signs from baseline); 4: Deterioration of symptoms/signs (including death due to NPSLE or complications of therapy).

A detailed description of the response criteria for each individual neuropsychiatric manifestation is given in Supplementary Table 2 (see Supplementary material). Clinical assessment was performed by a rheumatologist and occasionally by additional medical specialties. Specifically, we used the validated modified Rankin Scale (mRS) to quantify cerebrovascular disease (CVD)-related disability and dependence in daily activities [111]. Functional outcome at last follow-up was classified as good (mRS 0–2), moderate (mRS 3–4) or poor (mRS 5–6). Stroke recurrence while on CYC therapy was *per se* considered failure of treatment. In cases of myelopathy, we evaluated neurological impairment with the European Database for Multiple Sclerosis (EDMUS) grading scale (EGS), a validated tool for the clinical assessment of multiple sclerosis and neuromyelitis optica[112, 113]. An EGS score ≥ 3 was indicative of adverse neurological outcome. For the remaining manifestations, objective documentation of the response was done according to manifestation (eg. visual acuity in optic neuritis, auditory thresholds in sensorineural hearing loss, manual muscle testing ± electromyography in myelopathy etc).

For the evaluation of the harms related to CYC therapy, patient medical records were scrutinized for the documentation of neoplasias, amenorrhea/premature ovarian failure and serious infections, all evident after initiation of CYC treatment. Serious infections were defined as those occurring while the patient was receiving CYC or during one month after the last CYC dose and which necessitated intravenous antibiotics or hospitalization, or infections leading to death. Less severe infections not fulfilling these criteria were not recorded. Regarding amenorrhea, we specifically sought for its

occurrence in patients who were ≤ 45 years old when started on CYC therapy [age cut-off for gonadal protection with GnRH analogs] and was based on self-report by patients.

Statistical analysis: All data analyses were performed with IBM SPSS Statistics (version 21.0). Descriptive statistics were undertaken for continuous variables and median values/ranges were calculated. Chi-square or Fisher's exact test were used to compare categorical variables and the non-parametric Mann-Whitney U test was used to compare continuous variables. Statistical significance was indicated as a two-sided $p<0.05$.

3.3 Characterization of SLE patients with demyelinating features - Coexistence of SLE and MS: Originating from the finding that no NPSLE patients qualified for the ACR diagnosis of SLE demyelinating syndrome (see Results, **Table 4.2**), we atttempted to examine whether SLE patients with demyelinating features actually represent an overlap of SLE and MS.

The Rheumatology and Neurology Departments of the University Hospital of Crete have established independent electronic-based cohorts for patients diagnosed with SLE and MS, respectively. The SLE cohort is an inception cohort consisting of patients who fulfill either the updated 1997 ACR[8, 9] or the 2012 SLICC[10] criteria and who have undergone at least two consecutive evaluations in our centre during the period 1999-2012. MS patients are recruited from the MS Epidemiology Program Project of Crete, which has registered all incident MS cases in Crete during the years 1980-2012[114, 115]. The diagnosis of MS is based on the clinical and MRI criteria of the International Panel on MS (2010 McDonald criteria[96]). Demographic, socioeconomic, and past medical history data are recorded at baseline visit; clinical, laboratory, imaging data, and therapeutic changes are recorded at all visits.

For the purpose of the study, the two cohorts were scrutinized; patients diagnosed with both diseases or patients diagnosed with one disease (SLE or MS) who also had features suggestive of the other, were reevaluated to confirm or establish the diagnosis of SLE and MS, respectively. Patients were screened by one neurologist and one rheumatologist (PhD cand. AF). The identified SLE-MS overlap cases were followed with combined rheumatologic/neurologic evaluation on a regular basis at 3-6 month intervals, depending on disease activity, to determine natural course and prognosis. During patient follow-up, the SELENA-SLEDAI was used to define SLE disease activity and the SLICC damage index for SLE-associated damage. Progression of disability due to MS was assessed with the Expanded Disability Status Scale (EDSS).

Systematic review of the literature: We performed an additional English language literature review to identify additional cases of overlap between SLE and MS. We used the PubMed database from January 1980 to January 2013 with the following index terms: "multiple sclerosis" OR "myelitis" OR "myelopathy" OR "demyelinat*" AND "SLE" OR "lupus" (terms present in title or abstract). Original articles, case series and case reports were included in the search. Retrieved articles were further scrutinized based on abstract and/or full-text content. Relevant articles identified by manual search within the reference list of the originally retrieved publications were also included. We

included only cases in which the treating physicians had decisively reached a clinical diagnosis of both SLE and MS. We excluded cases of SLE-associated demyelinating syndrome (formerly referred to as "lupoid sclerosis") or cases of SLE with neuromyelitis optica (NMO), a disease previously considered to represent an MS variant with optic neuritis and longitudinal transverse myelitis, but recently established as a distinct entity characterized by the presence of antibodies against aquaporin-4[116].

4. RESULTS

4.1 Characterization of the NPSLE cohort and comparison of usual clinical care with the EULAR recommendations

Patients and neuropsychiatric events

We identified 94 patients who experienced a total of 123 lupus-related neuropsychiatric events (n=71 patients with a single event, n=17 with two events, n=6 with three events) (**Table 4.1**). At the time of the neuropsychiatric event, at least one of the EULAR-defined risk factors for primary NPSLE (previous NPSLE, generalized disease activity and aPL positivity) was present in almost 80% of events. 35% of events occurred within the first year after SLE diagnosis (26% as presenting manifestation of the disease).

Neuropsychiatric events and accompanying clinical characteristics (aPL status, SLE activity and damage at the time of NPSLE occurrence) are listed in **Table 4.2**. Most prevalent events were cerebrovascular diseases (CVD) (n=21, 17.1%), cognitive dysfunction (n=18, 14.6%), intractable lupus headache and mood disorder (n=12 each, 9.8%), seizure disorder and transverse myelitis (n=11 each, 8.9%). Manifestations (excluding those with <5 registered cases) accompanied by the highest generalized (non-neuropsychiatric) disease activity were psychosis and cognitive disorder, followed by myelopathy and CVD.

Brain MRI was performed in 75 neuropsychiatric events (61.0% of total events). In 21 of them (28.0%), MRI was considered normal; in the remaining cases, the most common finding was non-specific periventricular white matter hyperintensities (WMHIs, 40.8% of events), followed by cerebral infarcts (21.1%). Other diagnostic procedures included cerebrospinal fluid (CSF) analysis in 25 events, nerve conduction studies (NCS) in 14 and electroencephalogram (EEG) in 8 events.

Treatment of NPSLE included steroids (either initiation or escalation of previous dose) in 89 events (72.4%) and immunosuppressives in 73 events (59.3%). The latter included intravenous cyclophosphamide (42 cases), azathioprine (22 cases) and rituximab (5 cases). Antithrombotic therapy was administered in 41 neuropsychiatric events (antiplatelet agents in 30 and vitamin K antagonists in 11 cases), most commonly in ischemic CVD (**Table 4.3**).

Table 4.1 Demographic and clinical characteristics of 94 patients and 123 neuropsychiatric events.

Female, n (%)	84 (89.4)
Nationality, n (%)	
Greek	48 (51.1)
Romanian	46 (48.9)
Age at SLE onset (years), median (IQR)	37.0 (23.0)
Age at NPSLE (years), median (IQR)	42.0 (16.5)
Time lag between SLE onset and NPSLE occurrence (years), median (IQR)	4.0 (7.0)
NPSLE risk factors	
Generalized disease activity at neuropsychiatric event, n (%)	76 (61.8)
aPL (+) at neuropsychiatric event, n(%)	43 (35.0)
Previous severe neuropsychiatric event, n (%)	30 (24.4)
Any risk factor	96 (78.0)
SLEDAI at neuropsychiatric event, median (IQR)	8.0 (10.0)
Concomitant disease activity at neuropsychiatric event, n (%)	
Mucocutaneous domain	53 (68.8)
Musculoskeletal domain	51 (62.2)
Renal domain	16 (20.8)
Hematologic domain	23 (29.9)
SDI at neuropsychiatric event, median (IQR)	0.0 (1.0)
Medication received at the time of neuropsychiatric event	
Hydroxychloroquine	58 (47.2)*
Azathioprine	28 (22.8)
Methotrexate	8 (6.5)
Mycophenolate mofetil	5 (4.1)
Cyclophosphamide	3 (2.4)
Cyclosporine	2 (1.6)
Aspirin	24 (19.5)

NPSLE: Neuropsychiatric SLE; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index (SELENA); CNS: Central nervous system; SDI: Systemic Lupus International Collaborating Clinics (SLICC) Damage Index

* Of the remaining 65 events wherein patients were not receiving HCQ, in 32/65 (49.2%) the neuropsychiatric event was the presenting manifestation. The remaining 33/65 (50.8%) were due to non-compliance, thus contributing to the overall low frequency of HCQ use.

Table 4.2 Types of neuropsychiatric events, time lag from SLE onset, aPL status, total and non-neuropsychiatric activity and damage

Manifestation, n (%)	aPL (+), n (%)	Time lag from SLE onset (years), median (IQR)	Total SLEDAI, median (IQR)	Non-neuropsychiatric SLEDAI, median (IQR)	SDI, median (IQR)
CVD, 21 (17.1)	11 (52.4)	1.0 (8.0)	12.0 (5.7)	4.0 (5.7)	0.0 (1.0)
Cognitive disorder, 18 (14.6)	3 (16.7)	5.0 (6.2)	6.0 (4.7)	6.0 (4.7)	1.0 (1.0)
Lupus headache, 12 (9.8)	4 (33.3)	4.0 (6.7)	9.5 (9.5)	1.5 (9.5)	0.0 (0.0)
Mood disorder, 12 (9.8)	3 (25)	10.5 (13.7)	2.0 (6.0)	2.0 (6.0)	0.0 (1.0)
Seizure disorder, 11 (8.9)	2 (18.2)	7.0 (11.0)	8.0 (13.0)	0.0 (13)	0.0 (0.0)
Transverse myelitis, 11 (8.9)	3 (27.3)	2.0 (3.0)	4.0 (3.0)	4.0 (3.0)	0.5 (1.0)
Psychosis, 10 (8.1)	3 (30)	1.0 (7.5)	15.0 (9.5)	7.0 (9.5)	0.0 (0.5)
Cranial neuropathy, 8 (6.5) (II: 3, V: 2, VII: 2, III: 1)	4 (50)	2.0 (9.7)	11.0 (3.5)	3.0 (3.5)	0.5 (1)
Peripheral neuropathy, 6 (4.9)	3 (50)	5.5 (11.2)	2.5 (10.5)	2.5 (10.5)	0.5 (1.3)
Anxiety disorder, 5 (4.1)	1 (20)	2.0 (5.0)	3.0 (13.0)	3.0 (13.0)	0.0 (0.5)
Mononeuritis multiplex, 2 (1.6)	1 (50)	1.0 (0.0)	8.5[a]	8.5[a]	1.5[a]
Chorea, 2 (1.6)	1 (50)	4.5[a]	8.0[a]	8.0[a]	0.0 (0.0)
Aseptic meningitis, 2 (1.6)	1 (50)	2.5[a]	14.0 (0.0)	14.0 (0.0)	0.5[a]
Acute demyelinating polyradiculopathy, 1 (0.8)	1 (100)	0.0	7.0	7.0	1.0
Autonomic disorder, 1 (0.8)	1 (100)	2.0	6.0	6.0	1.0
Acute confusional state, 1 (0.8)	1 (100)	0.0	14.0	6.0	0.0

aPL: Antiphospholipid antibodies; CNS: Central nervous system; CVD: Cerebrovascular disease; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SDI: Systemic Lupus International Collaborating Clinics/ACR Damage Index - [a] Not possible to calculate IQR due to very low number of cases

Table 4.3 Imaging findings, therapeutic modalities and outcome in most common neuropsychiatric manifestations

Manifestation	Brain MRI	Most common MRI findings, n (%)	MRI interpretation, n (%)	aPL (+), n (%)	Immunosuppressive therapy, n (%)	Antiplatelet/Anticoagulation therapy, n (%)	Outcome at 6 months, n (%)
CVD	17/21[a]	Infarcts, 14 (82.3) WMHIs, 3 (17.6) Hemorrhage 1 (5.9)	Diagnosis-specific, 15 (88.2) Non-specific, 2 (11.8)	11 (52.4)	11 (52.4) *CYC 8* *AZA 4* *RTX 1*[b]	21 (100)	19 (90.5) improved 1 (4.8) worsened 1 (4.8) lost to follow-up
Cognitive disorder	13/18	WMHIs, 9 (69.2) Normal, 2 (15.4)	Non-specific, 13 (100)	3 (16.7)	8 (44.4) *AZA 4* *MTX 3* *CsA 1*	2 (11.1)	7 (38.9) improved 10 (55.6) stable 1 (5.6) lost to follow-up
Lupus headache	10/12	WMHIs, 5 (50) Normal, 5 (50	Non-specific, 10 (100)	4 (33.3)	6 (50.0) *AZA 4* *CYC 2*	4 (33.3)	7 (58.3) improved 4 (33.3) stable 1 (8.3) worsened
Mood disorder	4/12	WMHIs, 3 (75) Normal, 1 (25)	Non-specific, 4 (100)	3 (25)	3 (25.0) AZA 2 CYC 1	0 (0)	10 (83.3) improved 2 (16.7) stable
Seizure disorder	8/11	WMHIs, 4 (50) Normal, 3 (37.5) Atrophy, 1 (12.5)	Non-specific, 8 (100)	2 (18.2)	6 (54.5) *CYC 5* *AZA 1*	4 (36.4)	10 (90.9) improved 1 (9.1) stable
Transverse myelitis	5/11	WMHIs, 4 (80) Normal, 1 (20)	Non-specific, 5 (100)	3 (27.3)	10 (90.9) *CYC 7* *RTX 3* *MMF 1*[c]	3 (27.3) *2 aPL (+)*	10 (90.9) improved 1 (9.1) stable
Psychosis	3/10	Normal, 2 (66.7) WMHIs, 1 (33.3)	Non-specific, 3 (100)	3 (30)	7 (70.0) *CYC 5* *AZA 2* *RTX 1*[d]	3 (30) all aPL (+)	10 (100) improved
Cranial neuropathy	7/8	Nerve involvement, 2 (28.6) WMHIs, 4 (57.1) Normal, 2 (28.6)	Diagnosis-specific, 2 (28.6) Non-specific, 1 (71.4)	4 (50)	7 (87.5) *CYC 4* *AZA 2* *RTX 1*	3 (37.5)	5 (62.5) improved 3 (37.5) stable

[a] In the emaining 4 cases, brain computed tomography was performed and was diagnostic in 3 (infarcts) - [b] One patient received sequentially AZA, CYC and RTX
[c] One patient received combination of MMF and RTX - [d] One patient received CYC and RTX due to refractory psychosis
CVD: Cerebrovascular disease; MRI: Magnetic resonance imaging; WMHIs: White matter hyperintensities; aPL: Antiphospholipid antibodies; CYC: Cyclophosphamide; AZA: Azathioprine; MTX: Methotrexate; CsA: Cyclosporine A; MMF: Mycophenolate mofetil; RTX: Rituximab

In the majority of cases, the short-term outcome of NPSLE was favourable, with 96 events (78%) showing at least mild improvement and 22 (17.9%) remaining stable at 6 months. Manifestations with the most favourable course were psychosis, seizure disorder (the majority having resolved within 6 months) and transverse myelopathy (**Table 4.3**).

Comparison of routine care with the EULAR recommendations

In **Table 4.4**, we compare the EULAR recommendations (diagnosis and therapy) against the followed clinical care in the registered NPSLE cases. No statistically significant differences were observed between the two study centres. In addition, we did not observe statistically significant differences in terms of agreement with the EULAR recommendations, when neuropsychiatric events were stratified according to the time period (prior to or after 2010, year of publication of the EULAR recommendations) they occurred (**Table 4.5**).

- *Diagnostic work-up*

The EULAR recommendations advocate for the use of brain MRI in CVD, seizures, chorea and acute confusional state (ACS), and also in selected cases of cognitive dysfunction, myelopathy and psychosis (Supplementary Table 1, see Supplementary Material). Brain imaging was performed in 54/74 (73.0%) events in which it was recommended, as compared to 21/49 (42.9%) events this was not recommended (p=0.01). Notably, in the latter cases brain MRI was more likely to reveal no abnormalities [11/21 (52.4%) considered "normal" versus 10/54 (18.5%), p=0.008]. MRI was considered "specific for diagnosis" only in cases of CVD and also in two cases of cranial neuropathy (V and VII, one each). In all other cases, MRIs were considered as "non-specific or useful for exclusion of other causes" (infections etc) for the neuropsychiatric syndrome (Supplementary Table 2). The presence of non-specific WMHIs spanned the whole spectrum of neuropsychiatric events irrespective of the indication for MRI (p=0.80).

CSF analysis is specifically recommended by EULAR in cases of ACS, aseptic meningitis, myelopathy and inflammatory demyelinating polyradiculopathy, and it was carried out in 11/15 (73.3%) such events. However, lumbar puncture was also performed in events without clear recommendation, albeit less frequently [14/96 (14.6%) events, p<0.001]. These were cases of cranial neuropathy, psychosis, mood disorder and cognitive disorder. On all occasions, CSF analysis was performed to exclude alternative diagnoses, particularly infection; findings were suggestive of NPSLE albeit non-specific in all cases (pleocytosis and/or increased protein), with the exception of a single case of acute demyelinating polyradiculopathy in which results were typical (elevated protein with absence of pleocytosis).

Electroencephalogram (EEG) and nerve conduction studies (NCS) were generally undertaken in accordance with the recommendations [8/11 cases of seizures and 8/8 of peripheral neuropathy, respectively). NCS were also performed in more than half of myelopathy cases (6/11) to exclude alternative diagnoses, although this is not explicitly recommended.

Table 4.4 Concordance of clinical practice with the EULAR statements and recommendations

(For specific manifestations, applied in those with ≥ 8 events)

EULAR recommendations	Routine clinical practice, n (%)
General approach to NPSLE	
"The recommended MRI protocol (brain and spinal cord) includes conventional MRI sequences (T1/T2, FLAIR), DWI, and gadolinium-enhanced T1 sequences"	Performed in 76 events (61.8) *Diagnosis-specific only in CVD and cranial neuropathy*
"Glucocorticoids and immunosuppressive therapy are indicated for neuropsychiatric manifestations felt to reflect an immune/ inflammatory process (eg, ACS, aseptic meningitis, myelitis, cranial and peripheral neuropathies and psychosis) following exclusions of non-SLE-related causes"	33/41 (80.5) of "inflammatory events" received immunosuppressive therapy [vs. 39/82 (47.6) "non-inflammatory", p<0.001]
"Antiplatelet/anticoagulation therapy is indicated when manifestations are related to antiphospholipid antibodies, particularly in thrombotic CVD"[a]	9/12 (75) aPL (+) patients with such manifestations received antiplatelet/anticoagulation [versus 32/111 (28.8) in remaining events, p=0.002)
"The use of symptomatic therapies (eg, anticonvulsants, antidepressants) and the treatment of aggravating factors (eg, infection, hypertension and metabolic abnormalities) should also be considered"	Implemented in the vast majority: Psychosis: 10/10 (100) received antipsychotics - Seizures: 10/11 (90.9) anticonvulsants - Mood disorder: 12/12 (100) antidepressants - Anxiety disorder: 4/5 (80) anxiolytics
"Antiplatelet agents may be considered for primary prevention in SLE patients with persistently positive, moderate or high, antiphospholipid antibody titers"	7/31 (22.6) aPL (+) patients were receiving antiplatelets prior to NPSLE
CVD	
"Atherosclerotic/thrombotic/embolic CVD is common, hemorrhagic stroke is rare, and stroke caused by vasculitis is very rare in SLE patients; accordingly, immunosuppressive therapy is rarely indicated"	11/21 (52.4) of patients received immunosuppressive therapy
"Long-term anticoagulation should be considered in patients with stroke who fulfil the classification criteria for antiphospholipid syndrome for secondary prevention of recurrent stroke which commonly occurs"	7/11 (63.7) of aPL (+) patients with CVD received long-term anticoagulation
Cognitive dysfunction	
"Severe cognitive impairment…should be confirmed by neuropsychological tests in collaboration with a clinical neuropsychologist when available"	5/18 (27.8) underwent formal neurocognitive assessment to evaluate cognitive function
"Management of both SLE and non-SLE-associated factors as well as psycho-educational support may prevent further deterioration of cognitive dysfunction"	0/18 (0) received psycho-educational support

Seizures	
"The diagnostic work-up aims to exclude structural brain disease and inflammatory or metabolic conditions and includes MRI and EEG"	MRI was performed in 8/11 (72.8): "diagnosis non-specific" in all cases; EEG was performed in 8/11 (72.8): epileptiform changes in 3, normal in 5 cases
"In the absence of MRI lesions related to seizures and definite epileptic abnormalities on EEG following recovery from the seizure, withholding of AED after a single seizure should be considered. Long-term anti-epileptic therapy may be considered for recurrent seizures"	10/11 (90.9) received long-term antiepileptic drugs due to recurrent seizures or epileptiform EEG changes
"For most patients without generalized disease activity, immunosuppressive therapy is not indicated for prevention of recurrences or control of refractory seizures"	3/6 (50) received immunosuppressive therapy to prevent recurrent seizures despite the absence of generalized disease activity
"Anticoagulation may be considered in patients with aPL"	0/2 received anticoagulation (2/2 received antiplatelet therapy)
Mood disorder/Psychosis	
"There is no strong evidence to support the diagnostic utility of serological markers or brain imaging in major depression"	4/12 (33.3) underwent brain MRI: "diagnosis non-specific" in all cases
"Glucocorticoids and immunosuppressive therapy may be considered in SLE-associated psychosis, especially in presence of generalized disease activity"	7/10 (70) patients with psychosis received immunosuppressive therapy
Myelopathy	
"The diagnostic work-up includes gadolinium-enhanced MRI and CSF analysis"	Spinal MRI was performed and was diagnostic in 10/11 (90.9) and CSF analysis in 8/11 (72.8)
"Timely (as soon as possible) induction therapy with high-dose glucocorticoids followed by IV cyclophosphamide should be instituted"	High dose steroids were administered 11/11 (100) and IV cyclophosphamide in 7/11 (63.7) - Rituximab was administered in another 3/11 (27.3)
Peripheral neuropathy/Mononeuritis multiplex	
"Peripheral neuropathy often co-exists with other neuropsychiatric manifestations and is diagnosed with electromyography and NCS"	1/8 (12.5) co-existed with other neuropsychiatric manifestation (cognitive disorder) - 8/8 (100) were diagnosed with electromyography and NCS
"Combination therapy with glucocorticoids and immunosuppressive agents may be considered in severe cases"	7/8 (87.5) received immunosuppressive therapy (5 cyclophosphamide - 1 azathioprine - 1 cyclosporine)

[a] Apart from thrombotic CVD, these manifestations include chorea, ischemic optic neuropathy and refractory myelopathy (EULAR recommendations manuscript)
NPSLE: Neuropsychiatric SLE; CVD: Cerebrovascular disease; aPL: Antiphospholipid antibodies; MRI: Magnetic resonance imaging; ACS: Acute confusional state; EEG: Electroencephalogram; AED: Antiepileptic drugs; CSF: Cerebrospinal fluid; IV: Intravenous; NCS: Nerve conduction studies

Only 27.8% of patients (5/18) with cognitive dysfunction underwent the formal neuropsychological assessment recommended by EULAR [either the one-hour ACR battery or the computer-based automated neuropsychological assessment metrics (ANAM) system], due to lack of availability of neuropsychologists or time constraints. In the remaining cases, diagnosis was made with the Montreal Cognitive Assessment tool (MoCA), a one-page, performance-based questionnaire developed to identify cognitive impairment [117], and was attributed to SLE after the exclusion of alternative causes [median (IQR) MoCA score 20.0 (6.5), indicative of moderate dysfunction).

- *Therapy*

In accordance with the EULAR recommendations, immunosuppressants were administered more frequently in manifestations "felt to reflect an immune/inflammatory process", namely ACS, aseptic meningitis, myelitis, cranial and peripheral neuropathies and psychosis (80.5% vs. 47.6% in "non-inflammatory" events, $p<0.001$). Likewise, antiplatelet/anticoagulation therapies were instituted for events occurring in the presence of aPLs and are thought to be related to the latter, particularly ischemic CVD but also chorea, ischemic optic neuropathy and myelopathy refractory to immunosuppression (75% vs. 28.8% in events not considered to be related to aPLs, $p=0.002$) (**Table 4.4**).

Regarding CVD in particular, antiplatelet/anticoagulation was instituted in all 21 cases, with anticoagulation being reserved for patients fulfilling criteria for the antiphospholipid syndrome (7/11 of such cases received vitamin K antagonists). Interestingly, in more than half of CVD events (11/21, 52.4%), physician judgment advocated for the adjunctive use of immunosuppressive treatment; 7 patients were treated with cyclophosphamide (CYC), 4 with azathioprine (AZA) and one patient was treated sequentially with AZA, CYC and finally rituximab due to ongoing disease activity and severity of CVD. To further explore into this finding, we assessed levels of disease activity at the time of stroke. A total of 13/21 (61.9%) of CVD events occurred in the presence of generalized disease activity and immunosuppressive therapy was instituted in 9/13 (69.2%); major drivers of disease activity were mucocutaneous manifestations (8/13 events), arthritis (7/13), cytopenias (4/13), nephritis (3/13) and serological abnormalities (high anti-ds-DNA titres and/or low serum C3/C4) (6/13 events). No significant differences were found regarding patients' age and presence of traditional cardiovascular risk factors (smoking, diabetes, hypertension, dyslipidemia) between CVD events occurring in the presence or the absence of generalized disease activity (data not shown). The remaining 2/11 cases treated with immunosuppressives had low-level or no extra-CNS disease activity but suffered from CVD recurrence despite prior antithrombotic treatment. Median (IQR) non-neuropsychiatric SLEDAI at the time of stroke was significantly higher in cases that received immunosuppression compared to those that did not [6.0 (7.0) vs. 2.0 (4.0) respectively, $p=0.04$]. All patients (11/11, 100%) who received combined immunosuppression/antithrombotic treatment and 8/9 (88.9%) of those who received antithrombotic treatment alone had a favourable

outcome at 6 months (p=0.30).–In the two cases treated with immunosuppression due to CVD recurrence, no new recurrence was observed at 6 months.

Similar to diagnosis, the management of SLE patients with cognitive dysfunction was also not in accordance with the EULAR recommendations. Thus, none of the patients underwent psycho-educational interventions (cognitive rehabilitation) and the management of concomitant anxiety and depression was only rarely addressed (**Table 4.4**). Nonetheless, at 6 months, outcome of cognitive dysfunction was mostly stable (**Table 4.3**).

Table 4.5 Concordance of usual care with the EULAR recommendations for NPSLE stratified according to the timing of neuropsychiatric events

	Level of agreement, n(%)			
	Total study period (n= 105 events[1])	**Period 2001-2010 [2] (n=76 events)**	**Period 2011-2012 [2] (n=29 events)**	**p-value [3]**
Diagnostic work-up	103/150 [4] (68.7)	68/104 (65.4)	35/46 (76.1)	0.25
Treatment decisions	89/142 (62.7)	64/100 (64)	25/42 (59.5)	0.70

[1] Concordance rates calculated for a total of 105 events. Cases of lupus headache, autonomic neuropathy and anxiety disorder were excluded due to lack of detailed guidelines for diagnosis and treatment in the EULAR recommendations.

[2] EULAR recommendations for NPSLE were published in 2010

[3] Comparison of agreement rates between the 2001-2010 and 2011-2012 time periods

[4] Denominators in the Table indicate the total number of diagnostic or therapeutic interventions recommended by EULAR for all neuropsychiatric events included in the study. See also Supplementary Table 3 for more details.

4.2 Efficacy and safety of CYC for NPSLE

Neuropsychiatric manifestations, rationale for CYC administration and dosing schemes

CYC was administered in 50 neuropsychiatric events experienced by 46 patients; four patients received CYC for two distinct neuropsychiatric events with a time lag in-between ranging from 0 (concomitant events in two patients) to 48 months. Demographic characteristics of patients are shown in **Table 4.6**; there were no significant differences between the two study centres, with the exception of dosing scheme and cumulative dose of CYC (see below). Median age at NPSLE occurrence was 45 years (range 14-68 years), time lag from onset of SLE to NPSLE was 1.5 years (range 0-31 years), and 46% (23/50) of cases were tested positive for antiphospholipid antibodies at the time of neuropsychiatric involvement (one patient experienced CVD, thus fulfilling criteria for the antiphospholipid syndrome). Thirteen patients (28.2%) received CYC for a concurrent severe non-NPSLE manifestation (lupus nephritis in 12, severe thrombocytopenia in 1); characteristics of these patients were comparable to those of patients who received CYC primarily for NPSLE (data not shown).

Table 4.6 Demographic characteristics of NPSLE patients who received CYC in the two study centres.

Number of events (patients)	50 (46)
Gender, female, n (%)	40 (86.9)
Age at SLE onset, median (IQR)	38.0 (23.0)
Age at NPSLE occurrence, median (IQR)	45.0 (18.5)
aPL (+), n (%)	23 (46.0)
SLEDAI-2K at event, median (IQR)	13.0 (11.0)
Non-CNS SLEDAI-2K at event, median (IQR)	6.5 (10.0)
SDI at event, median (IQR)	0.0 (1)
SLEDAI-2K at last follow-up, median (IQR)	0.0 (2)
SDI at last follow-up, median (IQR)	1.0 (2)
Cumulative CYC dose, median (IQR)	7.2 (7.9)
Total number of CYC pulses, median (IQR)	8.0 (6.0)
Duration of follow-up, months, median (IQR)	46.5 (57.2)

NPSLE: Neuropsychiatric SLE; aPL: Antiphospholipid antibodies; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; CNS: Central nervous system; SDI: Systemic Lupus International Collaborating Clinics (SLICC) Damage Index

Most frequent manifestations were severe/refractory psychosis (12 cases), followed by axonal sensorimotor polyneuropathy (6 cases) and CVD, seizure disorder and cranial neuropathy (5 cases each) (**Table 4.7**). All NPSLE events were considered by treating physicians as indicative of an ongoing inflammatory process, thus justifying the use of immunosuppressive therapy. The choice of CYC was based on severity of the clinical syndrome and lack of response to symptomatic treatments. For CVD in particular, all five cases occurred in the presence of generalized SLE activity [median (IQR) SLEDAI-2K excluding the neuropsychiatric components: 6.0 (3.0)], and expert judgment advocated for the use of CYC despite the lack of solid evidence of frank cerebral vasculitis. One patient with CVD/APS was additionally treated with long-term anticoagulation; the remaining four received antiplatelets. Symptomatic therapy was also administered in all types of manifestations concomitantly with CYC, as per physician judgment and consultation of other medical specialties (eg. antipsychotics/antidepressants and anticonvulsants for psychosis/mood disorder and refractory seizures, respectively).

In all but two cases, CYC was administered as monthly intravenous pulses (the remaining two patients received oral CYC) and was chosen as first line immunosuppressive therapy in 42/50 of events (84.0%). In the remaining cases, CYC was used as second-line after failure of other immunosuppressants [azathioprine (AZA) in 6/8 events and methotrexate and steroid monotherapy in one event each)]. Both study centres used CYC in a protocol similar to lupus nephritis, ie. initial "induction phase" with monthly pulses for six months and subsequent evaluation for response and choice of maintenance therapy. Nevertheless, dosing of IV CYC differed between the two centres, based on local experience. In Heraklion, patients received the National Institutes of Health (NIH) lupus nephritis regimen, i.e. monthly 0.75-1 g/m2 IV for six months; two patients received the Euro-Lupus low-dose regimen (6x500 mg, 3 gr total) due to young age. In Cluj, patients generally received monthly CYC 15 mg/Kg for six months.

Cumulative CYC dose, duration of follow-up and outcome

The median number of CYC pulses per event was 8.0 (range 2-26 pulses) with a median cumulative dose of CYC of 7.2 gr (range 2.0-33.8 gr) (**Table 4.7**). Due to the higher doses of CYC used and the use of quarterly CYC pulses as maintenance therapy in some patients in the Heraklion cohort, cumulative per event dose of CYC was higher in this population (median 16.2 vs. 4.8 gr in the Cluj cohort, p=0.04). In the majority of events (43/50, 86.0%), patients received IV MP pulses before the first CYC pulse, with a median total dose 3.0 gr MP (range 0.5-3 gr).

Table 4.7 also shows the outcome of NPSLE cases at last follow-up, according to different manifestations. After a median follow-up of 46.5 months (range 5-408 months) following completion of CYC treatment, 23/50 (46.0%) of events had completely resolved (CR) and another 19 events (38.0%) had PR, according to the study definitions. No difference in response rates was observed

between the two centres (data not shown). Notably, higher CR rates were noted when CYC was prescribed as first-line treatment, (52.4% vs. 12.5% when used as second-line treatment, p=0.018). Among NPSLE syndromes with at least five cases, most favourable responses were observed in psychosis and seizure disorder, with a median (IQR) response on Likert scale at last follow-up of 1.0 (1.0) and 1.0 (1.5), respectively [CR/PR in 66.7/16.7%, and 60.0/20.0%, respectively).

In six cases, CYC therapy resulted in stabilization of symptoms/signs and two cases deteriorated. Rates of stabilization and no response were lower when CYC was used as first-line therapy (9.5% vs. 25.0% for stabilization and 2.4% vs. 12.5% for no response, respectively, p=0.018). Three events [CVD (stable), aseptic meningitis (deterioration), and psychosis (deterioration), one case each] received rescue treatment with rituximab, since response to CYC was considered unsatisfactory (**Table 4.7** for details).

Relapses - Maintenance therapy in cases that responded to CYC

Six patients (12.0%) experienced relapses of their initial NPSLE manifestation after initiation of CYC treatment. Three patients (aseptic meningitis, sensorineural hearing loss and psychosis, one case each) relapsed while on maintenance therapy (two with AZA, one with MTX), after a median (IQR) of 8.0 (1.5) months following completion of CYC pulses (one had CR, one PR and one stabilization). These patients were retreated with CYC and RTX and one patient eventually died of disseminated tuberculosis (see **Table 4.7** for details). The remaining three cases (two cases of seizure disorder and one CVD) relapsed within the first 6 months of CYC induction treatment. For both patients with seizure disorder, frequency of seizures was eventually reduced (both considered PR at last follow-up); relapse of CVD was deemed a treatment failure.

In patients who completed the induction phase without worsening (i.e. with PR/CR or stabilization) of their neuropsychiatric manifestation, maintenance immunosuppressive therapy commenced with AZA in 31 events (65.9%), bimonthly or quarterly pulses of intravenous CYC in 9 (19.1%), and mycophenolate mofetil (MMF) in 5 events (10.6%, all with concomitant lupus nephritis). Two patients did not receive any maintenance treatment. Among patients who achieved CR or PR, maintenance involved primarily AZA (38.0%), whereas prolonged CYC pulses were used by 12.0%; conversely, patients with stable NPSLE at last follow-up mainly continued with prolonged CYC pulses following induction (50.0%), whereas AZA was used by 33.0% (p=0.001 for the comparison between patients with CR/PR versus those with stable NPSLE).

Table 4.7 Neuropsychiatric manifestations, cumulative CYC dose, duration of follow-up and outcome of NPSLE treated with CYC, according to manifestation

Manifestation (n)	Cumulative CYC dose (gr), median (IQR)	Duration of follow-up (months), median (IQR)	Outcome at last visit, arbitrary 4-level scale, median (IQR) [a]	Specifications	Major complications
Psychosis (12)	5.9 (4.2)	41.5 (65.7)	1.0 (1.0)	▪ Complete resolution of psychotic features in 8 patients ▪ Significant improvement in 2 patients - one experienced moderate relapses and was given quarterly CYC pulses as maintenance therapy ▪ No response in one patient at 3 months - treated with RTX as "rescue therapy" and resolved completely	▪ One patient experienced reactivation of HBV infection ▪ One patient was admitted in ICU due to septic shock ten days after the first CYC dose
Polyneuropathy (6)	8.8 (9.5)	57 (53.5)	2.0 (0.2)	▪ Complete resolution of neuropathic symptoms in 1 patient ▪ Significant subjective improvement in 5 patients	(-)
CVD (5)	9.0 (9.9)	36.0 (91)	2.0 (2.0)	▪ Median mRS: 1 [b] ▪ Recurrence of stroke in one patient ▪ One patient was treated with RTX after 6 pulses of CYC 500 mg due to ongoing smoldering disease activity	(-)
Seizures (5)	4.8 (7.0)	34.0 (58.5)	1.0 (1.5)	▪ Complete disappearance of seizures in 3 patients ▪ Reduction in seizure frequency in 2 patients (one experienced seizure relapses while on CYC therapy but eventually responded with decreased frequency)	(-)
Cranial neuropathy (5)	22.1 (25.4)	61.0 (30.5)	3.0 (1.0)	▪ Sensorineural hearing loss (1 patient): Near complete restoration of auditory function; see **Fig. 4.1**) ▪ Optic neuropathy (3 patients): Patient 1 unilateral left optic neuropathy - improvement of visual acuity from baseline finger counting to 2.5/10 after therapy - Patient 2 unilateral left optic neuropathy - no response in left eye after therapy (light perception) - Patient 3 unilateral right optic neuropathy - improvement of visual acuity from baseline finger counting to 3/10 after therapy ▪ Trigeminal neuritis (1 patient): No response	(-)
Myelopathy (4)	9.6 (8.9)	51.5 (82.7)	1.5 (1.0)	▪ Complete sensorimotor recovery in 2 patients ▪ Significant improvement in 2 patients ▪ Median EGS: 2.0	(-)
Mononeuritis multiplex (4)	4.2 (11.8)	94.0 (66.0)	1.0 (1.0)	▪ Complete recovery of motor strength in 3 patients ▪ Significant improvement in 1 patient	(-)

Aseptic meningitis (3)	2.2[c]	8.0[c]	1.0[c]	▪ Complete remission in two patients ▪ 3rd patient: Initial complete response to CYC - Relapse while on AZA maintenance therapy - retreatment with CYC and RTX ("rescue")	▪ 3rd patient: Death from disseminated tuberculosis 2 months after RTX administration
Headache (2)	5.8[c]	49.0[c]	1.5[c]	▪ Disappearance of headache in one patient and partial improvement in another	(-)
Acute confusional state (1)	3.6	67	1	▪ Complete resolution of symptoms	(-)
Acute demyelinating polyradiculopathy (1)	6.0	4	2	▪ Partial recovery of motor strength	(-)
Mood disorder (1)	21.7	34	2	▪ Partial improvement in mood - resolution of accompanying psychotic features	(-)
Severe cognitive disorder (1)	4.8	43	2	Partial improvement in visual and verbal learning and memory, and affective decision making and response control	(-)

CYC: Cyclophosphamide; RTX: Rituximab; CVD: Cerebrovascular disease; HBV: Hepatitis B virus: mRS: modified Rankin Scale; EGS: EDMUS Grading Scale; AZA: Azathioprine

[a] Physician judgment-based 4-level scale: 1: Complete response (disappearance of initial symptoms/signs that prompted use of CYC); 2: Partial response (significant improvement without disappearance of initial symptoms/signs); 3: Stabilization (absence of clinically significant change in symptoms/signs from baseline); 4: Deterioration of symptoms/signs (including death) - for more details regarding response per specific neuropsychiatric manifestation, see Supplementary Table 1.

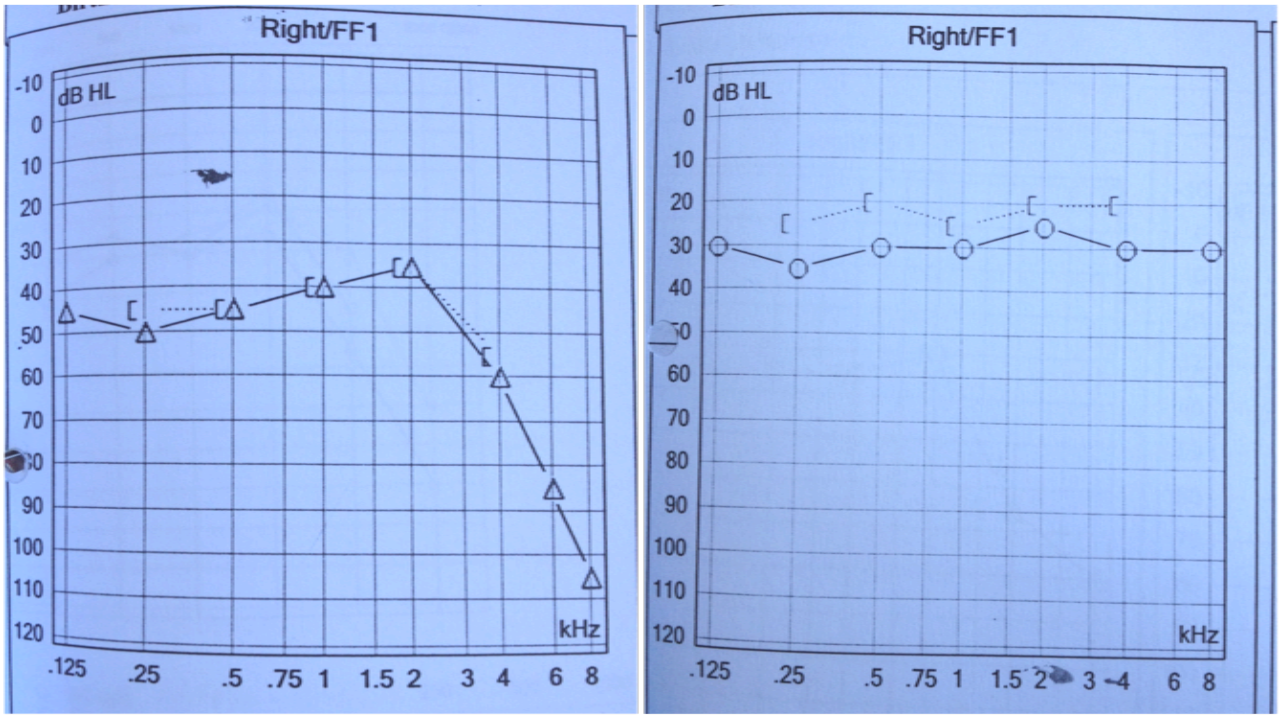
[b] Modified Rankin Scale: 0: No symptoms at al; 1: No significant disability despite symptoms; able to carry out all usual duties and activities; 2: Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance; 3: Moderate disability; requiring some help, but able to walk without assistance; 4: Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance; 5: Severe disability; bedridden, incontinent and requiring constant nursing care and attention; 6: Dead - *Categorization: mRS 0–2= Good, mRS 3–4= Moderate, mRS 5–6= Poor functional outcome*

[c] Not possible to calculate IQR values

Side-effects

No malignancies were observed during follow-up. Three cases of serious infections occurred: one reactivation of hepatitis B virus, one fatal case of disseminated tuberculosis and one respiratory infection with septic shock necessitating admission to intensive care unit (**Table 4.7**). Regarding gonadal toxicity, 23 female patients (16 in Cluj - 7 in Heraklion) were ≤ 45 years old when they started receiving CYC for their neuropsychiatric syndrome. The two centres differed in their practice regarding gonadal protection during CYC therapy. In Heraklion, except of the two patients who received the low-dose Euro-Lupus protocol, the rest received gonadal protection with GnRH analogs; patients in Cluj did not receive such protection. Secondary amenorrhea was recorded in three patients, all from Cluj. Two patients had received IV pulses (cumulative dose 5.4 and 8.0 gr, respectively) and the third one oral CYC.

Figure 4.1. Pure tone audiogram of severe relapsing unilateral sensorineural hearing loss before and after treatment with IV CYC. Note the markedly diminished audiometric thresholds at higher frequencies (*left*), almost completely reversed after CYC therapy (*right*).



4.3 Characterization of SLE patients with demyelinating features - Coexistence of SLE and MS

Case summary

From our cohorts of 728 patients with SLE and 819 patients with MS, we identified a total of nine patients who fulfilled both the criteria for SLE and MS, corresponding to a prevalence rate of 1.0–1.2%. The detailed demographic and clinical characteristics of the patients are presented in **Table 4.8**. All patients were Caucasian women, with a median age of SLE diagnosis at 40 years [interquartile range (IQR) 8 years], which tends to be higher than the usual age of disease presentation. Likewise, in eight cases with SLE and relapsing remitting MS (RRMS) type, the median age at MS onset was 36 years (IQR 12), which exceeds almost by six years the average age of the whole RRMS patient cohort [115]. In five patients, the diagnosis of SLE preceded the development of MS with a time lag of up to 5 years (median: 4 years). In the remaining four patients the diagnosis of MS was established before the appearance of lupus features (median lag: 5.5 years); one patient with a long-standing history of RRMS developed SLE more than 20 years after MS diagnosis. Antiphospholipid antibodies (aPLs) were present in low titers in 2 patients (22%, both confirmed 12 weeks apart), but none of them fulfilled the criteria for antiphospholipid syndrome. Specific antibodies against extractable nuclear antigens (anti-SSA/SSB, anti-Sm) were not detected in any patient.

All patients had mild SLE features with cutaneous, mucosal and musculoskeletal manifestations, only a single patient had a history of pericarditis and major manifestations (i.e. renal, neuropsychiatric or hematologic) were not observed. Photosensitivity, a feature present in all nine patients, was defined according to the 1987 ACR criteria case definition, with a physician-documented erythematous rash in sun-exposed areas. Regarding the presentation of MS, initial neurologic manifestations stemming from the spinal cord were observed in seven patients (78%); One patient presented with sensorimotor symptoms and another with optic neuritis.

Brain magnetic resonance imaging (MRI) revealed small (< 1cm), focal, discrete or coalescent infra- and supratentorial, T2 hyperintense lesions in all patients. As shown in **Table 4.9**, the anatomic distribution of these lesions fulfilled the MRI criteria for DIS, according to the International Panel on MS (2010 McDonald criteria [97]). Additional imaging findings specific for MS were also present (**Figure 4.1**), including: a) periventricular ovoid lesions (Dawson's fingers), with typical periventricular location, (**Figure 4.1 B**) in all patients, b) lesions adjacent to the temporal horns in 8 out of 9 patients, c) lesions in corpus callosum radiating away from the callososeptal interface (**Figure 4.1 D**) in 7 out of 9 patients, and d) coexistence of iso- and hypo-intense lesions on T1 sequences at the baseline MRI, indicative of different amount of demyelination and axonal loss, present in all patients. Spinal MRIs revealed focal lesions at the posterolateral portion of the cervical and/or thoracic spinal cord, indicative of MS (**Figure 4.1 A**), in 8 out of 9 patients. DIT was documented by the simultaneous presence of enhancing and non-enhancing lesions at baseline MRI in 4 out of 9 patients, and/or new T2 hyper-intense lesions in subsequent MRI scans in all nine patients.

Table 4.8 Clinical characteristics of SLE-MS patients in our cohort

Patient	Age at diagnosis of SLE/MS	SLE manifestations [Set/No. of SLE criteria]	aPLs	Therapy for SLE	SDI	Type of MS	Type of first symptom of MS	Therapy for MS	Progression of EDSS score	MS relapses	Follow-up (years)
1	40/56	Photosensitivity, arthritis, leukopenia, ANA(+) [ACR/4; SLICC/4]	(-)	HCQ, AZA	0	RRMS	Spinal	Natalizumab	4.5→5.5	0	1
2	44/21	Photosensitivity, malar rash, arthritis, mouth ulcers, aPL(+) [ACR/5]	aCL(+)[1]	HCQ, CS	0	RRMS	Spinal	Interferon β	2.5→2.5	6	2
3	36/40	Photosensitivity, arthritis, pericarditis, mouth ulcers, ANA(+) [ACR/5; SLICC/5]	(-)	HCQ, AZA, MTX	0	RRMS	Spinal	Interferon β, Rituximab	2.0→2.5	2	7
4	34/39	Photosensitivity, malar rash, arthritis, hair loss, aPL(+) [SLICC/4]	aβ2GPI(+)[2]	HCQ	0	RRMS	Spinal	Interferon β	2.5→2.5	1	1
5	55/57	Photosensitivity, arthritis, mouth ulcers, ANA(+) [ACR/4; SLICC/4]	(-)	HCQ, CS	0	RRMS	Sensorimotor	CS	3.5→4.5	6	6
6	56/60	Photosensitivity, malar rash, arthritis, ANA(+) [ACR/4]	(-)	HCQ	0	PPMS	Spinal	CS, AZA, Glatiramer acetate	3.5→6.0	NA	10
7	36/34	Photosensitivity, malar rash, chronic urticaria, arthritis, ANA(+), ↓C3/C4 [ACR/4; SLICC/4]	(-)	HCQ, AZA	0	RRMS	Spinal	Interferon β	2.0→2.0	1	4
8	42/36	Photosensitivity, arthritis, leukopenia, ANA(+) [ACR/4; SLICC/4]	(-)	HCQ	0	RRMS	Optic neuritis	Glatiramer acetate	2.0→2.0	8	10
9	35/30	Photosensitivity, malar rash, arthritis, ↓C3/C4, ANA(+) [ACR/4; SLICC/4]	(-)	HCQ	0	RRMS	Spinal	Interferon β	0.0→3.0	8	5

EDSS, Expanded Disability Status Scale; RRMS, Relapsing remitting MS; PPMS, Primary progressive MS; HCQ, Hydroxychloroquine; CS, Corticosteroids; AZA, Azathioprine; ANA, Antinuclear antibodies; aPL, Antiphospholipid antibodies; aβ2GPI, Antibodies to β2GPI; aCL, Anticardiolipin antibodies; ACR, 1987 revised American College of Rheumatology classification criteria; SLICC, 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria; SDI, SLICC Damage Index; NA, Not applicable

[1] aCL titer: 30 IgG phospholipid units /ml (normal values <20 IgG phospholipid units/ml)

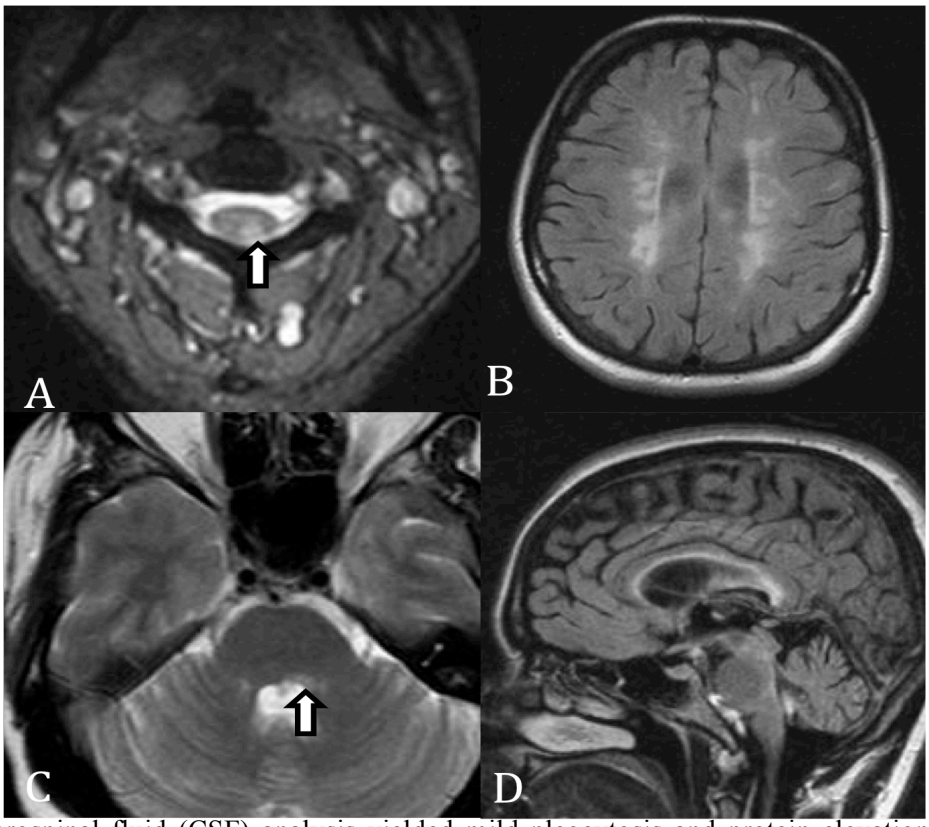
[2] aβ2GPI titer: 28 U/ml (normal values <20 units/ml)

Table 4.9 Anatomic distribution of the MRI lesions identified in the SLE-MS patients of our cohort

Patient	Pons	Cerebellar Peduncles	Midbrain	Cerebellum	Periventricular	Corona radiata	Semioval center	Subcortical	Juxtacortical	Corpus callosum	Deep gray matter (thalami, basal ganglia)	Spinal cord
1	-	-	+	-	++	+	+	++	+	-	-	+
2	+	-	+	+	++	+	+	++	++	-	+	+
3	+	+	-	+	+++	+++	+++	++	+	+	+	+
4	+	-	-	-	++	+	-	++	++	+	-	+
5	+	+	-	-	+	+	+	+	+	+	-	+
6	+	+	+	-	++	++	+	++	++	+	+	+
7	-	+	+	-	+	+	-	+	+	+	+	-
8	+	-	+	-	++	+	+	+	+	+	-	+
9	+	+	-	-	+	+	+	+	-	+	-	+

+: less than 5 lesions, ++: 5-10 lesions, +++: more than 10 lesions.

Figure 4.1 Representative figure of a patient (case 3, Table 4.8) with SLE and MS coexistence. MRI of the spine with T2 sequence in axial plane reveals a hyperintense lesion at the left posterolateral portion of the cervical spinal cord (A, arrow). MRI of the brain with FLAIR sequence in axial (B) and sagittal (D) planes and T2 sequence in axial plane (C), show multiple, hyperintense lesions at the periventricular and subcortical white matter and also at the corona radiata (B), the left posterior part of the upper pons (C, arrow) and the corpus callosum (D). The imaging characteristics and anatomic distribution of the lesions indicate demyelinating disease with DIS, typical of MS.



Cerebrospinal fluid (CSF) analysis yielded mild pleocytosis and protein elevation in four patients (44%), whereas intrathecal production of immunoglobulins (either increased IgG index or presence of oligoclonal bands) was observed in six patients (67%). Transcranial magnetic stimulation of the cortex was abnormal (evidence of pyramidal track involvement) in 5/9 patients (56%), visual evoked potentials (VEP) showed evidence of optic neuritis (either subclinical or clinical) in 4/8 patients (50%) and somatosensory evoked potentials (SSEP) were abnormal (i.e. evidence of posterior column dysfunction) in 2/6 (33%).

Five patients (55%) were treated with interferon-β (IFN-β) for control of their neurological symptoms. Two patients (case 7 and case 9, **Table 4.8**) were diagnosed with SLE after IFN-β administration (the former, 2 ½ years after IFN-β initiation presented with fatigue, prominent arthritis and ANA positivity, whereas the latter, 1 ½ years after IFN-β initiation developed prominent chronic urticaria and hypocomplementemia). However, a targeted history revealed that lupus features (photosensitivity, fatigue, arthralgias) were evident prior to the initiation of IFN therapy and attribution to the drug was not established after reaching consensus. IFN-β was nevertheless discontinued in the second patient due to the severity of urticaria, necessitating high dose of steroids.

In the case of the three patients who received IFN-β treatment after SLE had been diagnosed, the decision was based on multidisciplinary (neurologic/rheumatologic) consensus that: a) their lupus was mild and had been quiescent for more than 6 months, b) the severity of the neurologic (MS) syndrome warranted treatment with an approved agent of established efficacy, and c) the patients would be under close follow-up (monthly for the first 3 months and then every 3 months) for prompt identification of any signs and symptoms suggestive of SLE flare. None of the patients experienced a lupus flare after several months of follow-up (12, 11 and 6 months, respectively). Other therapeutic modalities for MS included glatiramer acetate (two patients, 25%), natalizumab and rituximab (one patient each); the latter is reserved for refractory cases with evidence of activity from both diseases, as it is currently off-label for both SLE and MS. SLE treatment consisted of hydroxychloroquine in all patients and occasional short courses of steroids; addition of a second disease-modifying drug (azathioprine or methotrexate) to control disease activity was considered necessary only in three (33%).

The clinical outcome of MS varied; during a median follow-up of 4 years (range 1-10 years), three patients remained stable, whereas the remaining experienced deterioration in disability. MS relapses were not uncommon with a median (IQR) of 4.0 (5.5) relapses per patient. Nevertheless, disability progression at the end of follow-up as calculated by the EDSS score was mild [median (IQR) EDSS increase 0.5 (1.0)] with 6/9 patients showing only residual neurologic symptoms but minimal disability (EDSS≤ 3.0). In all patients, SLE disease activity remained generally low to moderate (SLEDAI ≤ 6) and no damage accrual was noted.

Systematic literature review

Figure 4.2 illustrates the flow diagram of the systematic literature search performed for the identification of the relevant studies. The systematic literature search identified detailed reports of 9 cases of SLE/MS coexistence[118-123]. Of note, most studies were published prior to the era of widespread use of MRI, the use of the McDonald diagnostic criteria for MS and the full characterization of the NMO entity. Consequently, this raises the possibility of potential misdiagnosis if current diagnostic work-up and classification criteria were to be used a posteriori. To this end, we included only cases for which the physician consensus at the time of evaluation had reached the diagnosis of definite MS. Demographics and clinical characteristics are provided in **Table 4.10**. All patients were female, the vast majority of Caucasian ancestry and, similarly to our cohort, none fulfilled criteria for APS. RRMS was the most common MS type (66%), but manifestations at MS onset were more diverse compared to our cohort. In the 9 published cases, MS preceded the development of SLE, contrary to our findings wherein the majority (55%) of patients experienced MS symptoms following the diagnosis of SLE. As such, median age at MS diagnosis was markedly different (39.5 years in our cohort as compared to 29.5 years in the published cases),

while SLE diagnosis was established at comparable ages (40 years in our cohort versus 39 years in published cases). Unlike our patients who carried a mild SLE phenotype, cases from the literature tended to have more severe SLE, with three patients having at least one major manifestation including CNS, renal and severe hematologic disease. The lack of detailed description on laboratory parameters, treatment modalities, duration of follow-up and outcome in many of these reports precluded any further comparisons (**Table 4.11**).

Figure 4.2 Flow diagram of the systematic literature review

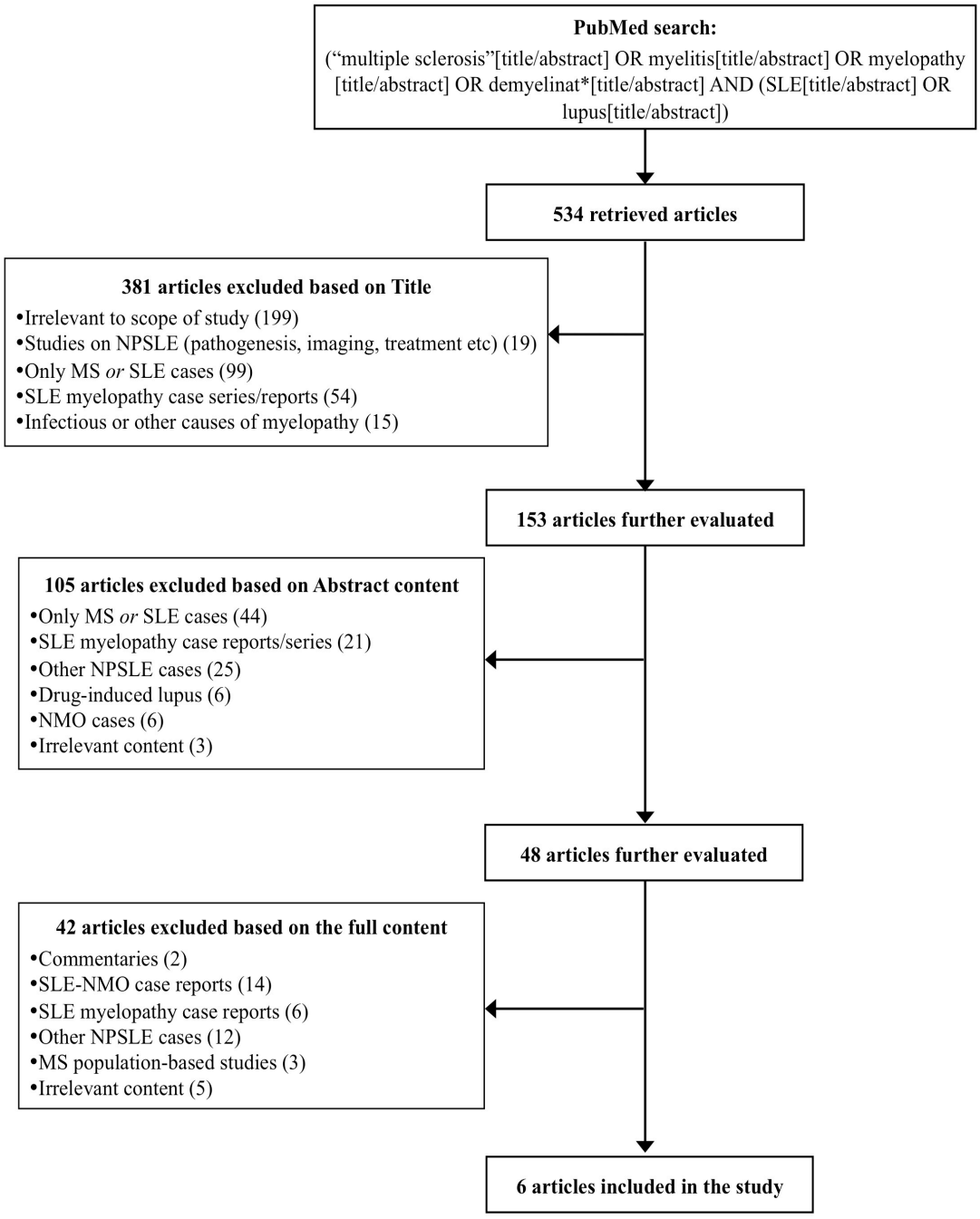


Table 4.10 Summary of published SLE-MS overlap cases in the literature.

Case (Reference)	Age at diagnosis of SLE/MS	SLE manifestations	aPLs	Therapy for SLE	Type of MS	Type of first symptom of MS	Therapy for MS	MS relapses
Case 1[119]	58/37	Scarring alopecia, leukopenia, ANA(+)	NR	Topical CS	RRMS	Polysymptomatic	ACTH, Probanthine	NR
Case 2[121]	44/32	Serositis, arthritis, leukopenia, hematuria, ANA(+)	NR	CS	RRMS	Sensorimotor	NR	NR
Case 3[121]	34/30	Photosensitivity, serositis, nephritis, arthritis, ANA(+), anti-dsDNA(+)	NR	NR	RRMS	Brainstem	NR	NR
Case 4[121]	57/29	Arthritis, ANA(+), anti ds-DNA(+), ↓C4	(-)	NR	SPMS	Optic neuritis	NR	NR
Case 5[123]	53/45	Transverse myelitis, thrombocytopenia, ANA(+), anti-dsDNA(+), ↓ C3/C4	aCL (+) LA (+)	CS, Plasma exchange	RRMS	Optic neuritis	CS, carbamazepine	4
Case 6[118]	11/10	Photosensitivity, malar rash, interstitial nephritis, ANA(+), anti-dsDNA(+)	NR	CS	RRMS	Spinal	CS	7
Case 7[120]	NR	Arthritis, oral ulcers, ANA(+), anti-dsDNA(+)	(-)	NR	PPMS	Spinal	NR	NA
Case 8[120]	26/21	Arthritis, Thrombocytopenia, ANA(+), anti-dsDNA(+)	aβ2GPI (+)	CS	PPMS	Spinal	NR	NA
Case 9[122]	32/14	Malar rash, arthritis, ANA(+), anti-dsDNA(+)	(-)	CS, HCQ, ASA	RRMS	Polysymptomatic	No therapy	5

aPLs, Antiphospholipid antibodies; CS, Corticosteroids, HCG, Hydroxychloroquine; ASA: Acetylsalicylic acid; aCL, Anticardiolipin antibodies; LA, Lupus anticoagulant; aβ2GPI, Antibodies to β2GPI; RRMS, Relapsing remitting MS; PPMS, Primary progressive MS; SPMS, Secondary progressive MS; ACTH, Adrenocorticotropic hormone; NR, Not reported; NA, Not applicable

Table 4.11 Comparison of clinical features between our cohort and previously published cases of SLE/MS coexistence

	Our cohort	Published cases
Gender (female)	9/9 (100%)	9/9 (100%)
Race (Caucasian)	9/9 (100%)	7/9 (78%)
SLE diagnosis prior to MS	5/9 (55%)	0/9 (0%)
ANA (+)	7/9 (78%)	9/9 (100%)
aPLs (+)	2/9 (22%)	2/5 (40%) [a]
Age at SLE diagnosis [median (IQR)]	40 (8)	39 (24)
Age at MS diagnosis [median (IQR)]	39 (24)	30 (14)
No. ACR criteria for SLE [median (IQR)]	4 (0)	4 (2)
Major SLE manifestation [b]	0/9 (0%)	3/9 (33.3%)
Type of MS (RRMS)	8/9 (88.9%)	5/8 (62%) [a]
Most common initial MS manifestation	Spinal (78%)	Spinal (33%)
Fully ambulatory at last follow-up (EDSS $\leq$ 4.5)	7/9 (78%)	5/9 (5%)

RRMS, Relapsing remitting MS; aPLs, Antiphospholipid antibodies; ANA, Antinuclear antibodies; IQR, Interquartile range

[a] Not reported in the rest of the cases

[b] Includes renal, CNS or severe hematologic disease

5. DISCUSSION

5.1 Characterization of the NPSLE cohort and comparison of usual clinical care with the EULAR recommendations

The ACR nomenclature and case definitions for NPSLE improved the characterization of this challenging entity; however, lack of specificity and uncertain clinical significance of subtle manifestations often make the attribution of neuropsychiatric symptoms to SLE difficult. In view of the paucity of high-level evidence, diagnostic and therapeutic decisions in NPSLE are largely based on physician judgment. The EULAR recommendations combined existing evidence and expert consensus, in an effort to facilitate management of NPSLE especially in places that lack adequate expertise. Nevertheless, guidelines carry the inherent problem of being unable to capture all aspects of clinical practice at all times. To this end, we attempted to juxtapose real-life management of SLE patients with neuropsychiatric manifestations in two experienced centres with the EULAR recommendations, and identify areas that may require additional attention.

Notably, the time period of our study predominantly included events that occurred before the publication of the EULAR recommendations in 2010. In this regard, the overall good concordance rates between usual care and the recommendations and the absence of a significant difference in this concordance between events occurring prior and after publication of the recommendations is a reassuring observation, as the management of NPSLE has traditionally been based on expert opinion. Moreover, the outcome of NPSLE patients was generally ~~favourable~~, in accordance with previous reports[48, 124].

A number of interesting observations were made through the comparison of the EULAR recommendations with routine clinical practice in NPSLE patients. First, brain MRI was performed in excess as part of the diagnostic work-up; in cases where its use is not recommended by EULAR, it often failed to reveal any abnormalities and was not useful for diagnosis and management. Neuroimaging with MRI is considered a *sine qua non* in the diagnostic work-up of NPSLE. Despite general agreement for its utility, lack of "specificity" of conventional MRI remains an issue. Indeed, the percentage of "normal" brain imaging in our cohort was substantial (~28%), albeit smaller than reported in other recent studies (42%-58%) [65, 69]. Specific MRI lesions were present only in cases of CVD and in isolated cases of cranial neuropathy. The most frequent non-specific abnormal MRI finding, periventricular and brainstem WMHIs, was present across all types of manifestations, focal or diffuse, central or peripheral. WMHIs are insufficient to guide therapeutic decisions, as they are also present in SLE patients without neuropsychiatric manifestations and healthy middle-aged individuals [66, 125, 126]. However, their presence could imply ongoing small vessel disease in SLE and their incidental detection in lupus patients may dictate aggressive control of traditional cardiovascular risk factors including hypertension and hypercholesterolemia. In this regard, an MRI

with white matter pathology, although not specific for diagnosis, can be considered useful in some instances. Conventional MRI will thus remain the procedure of choice for NPSLE, especially for the exclusion of alternative diagnoses. However, as NPSLE is not a uniform entity, application of brain MRI should not follow a "one size fits all" approach. Adherence to the EULAR guidelines in this regard, provides a useful guide to avoid unnecessary imaging and normal results, in cases where it has no clear indication (e.g. mood disorders or disorders of the peripheral nervous system). The same holds true for other diagnostic procedures such as spinal MRI, EEG and NCS, which have an even narrower range of indications.

An important finding of our study was that 62% of CVD cases occurred in the presence of generalized disease activity and immunosuppressive therapy (including CYC) was given to most of these patients. Optimal management of stroke in the context of active lupus represents a challenge. Acute CVD management should follow the recommendations for the general population, after consultation with a stroke specialist [79]. Secondary prevention includes antiplatelets or anticoagulation in cases of aPL-associated thrombotic CVD. However, occurrence of non-embolic CVD in a patient with active/flaring SLE could raise the possibility of concurrent inflammatory component in the atherothrombotic process. SLE *per se* is considered an independent risk factor for accelerated cardiovascular disease [127] and a recent study showed increased endothelial dysfunction in active SLE which was reversed after immunosuppressive therapy [128]. Thus, in clinical practice and especially in the absence of aPL positivity or pathognomonic MRI findings, the "inflammatory" and "thrombotic/ischemic" states in NPSLE are not always possible to differentiate or they may coexist. To this end, immunosuppressive therapies, along with antiplatelets/anticoagulation, could be considered to reduce the disease inflammatory burden and its pro-atherothrombotic effects. Our short-term data and unpublished experience with longer follow-up of these patients suggest good outcomes with minimal rates of CVD recurrence. Nevertheless, prospective studies are needed to define the natural history of CVD in the context of SLE, in case antithrombotic therapy is combined with immunosuppression or not.

A major source of "discordance" between the EULAR recommendations and routine clinical practice concerned the diagnosis and management of cognitive dysfunction in SLE patients. Although this represents one of the most frequent neuropsychiatric manifestations (up to 80% in some cohorts [26]), the majority of cases have only subtle or mild cognitive deficits that tend to follow a benign course, and only a minority (3-5%) will develop severe cognitive impairment [129, 130]. Although the EULAR recommends the ACR one-hour formal battery of neuropsychological tests or the computer-based ANAM for the assessment of cognitive function in patients with SLE, both modalities are time-consuming and require special training, which limit their widespread use in routine clinical practice. Recent studies have attempted to validate simpler screening tools as more convenient and suitable for routine care. While the Cognitive Symptom Inventory questionnaire failed to show association with the ANAM [131], application of the MoCA questionnaire in a small study showed good

correlation with ANAM scores, with a sensitivity of 83% [132]. We believe that a simple tool such as the MoCA, due to its user-friendly nature and ease of application, may serve for screening of cognition defects in everyday clinical care. Patients with possible cognitive deficits who fail the cut-off limit should nevertheless be referred for detailed neuropsychological evaluation.

Our study has certain limitations. First, because of its retrospective nature, it cannot be viewed as a validation study. This remains to be performed in a prospective manner. Second, due to the lack of a "gold standard" for NPSLE diagnosis, it is not possible to calculate sensitivity and specificity values for the EULAR risk factors [133]. Third, the high concordance rates with the EULAR recommendations may be biased by the fact that both study centres are tertiary referral centres with experience in the management of patients with NPSLE. Last, some of the ACR case definitions were underrepresented or not represented at all in our cohort.

In summary, we reported the first comparison between real-life clinical care of NPSLE patients and the evidence-based/expert consensus EULAR guidelines. Due to its nonspecific and complex presentation, the management of NPSLE will continue to rely on multidisciplinary collaboration and experienced physician intuition. Nevertheless, for centres with less experience in SLE, the EULAR recommendations provide a useful, albeit imperfect, framework for the initial management of patients with neuropsychiatric involvement.

5.2 Efficacy and safety of CYC for NPSLE

Treatment of NPSLE is plagued by scarcity of high-quality evidence to guide therapeutic decisions, owing to its rarity as well as to the heterogeneity of manifestations that hinder the design and conduction of RCTs. As highlighted in a recently updated Cochrane systematic review [134], only a single RCT has been performed in NPSLE, which has shown superiority of IV CYC over IV MP [135]. In that study, 94.7% of patients that received IV CYC experienced at least a 20% improvement in their baseline clinical, serological, and specific neurological measures after two years, as compared to 53.8% of those who received IV MP. Nevertheless, the low number of patients (32 in total) precluded the extraction of more solid conclusions. A number of earlier uncontrolled studies have also supported the use of CYC in various inflammatory neuropsychiatric manifestations, including myelopathy and cranial neuropathies, acute confusional state and peripheral nervous system disorders [135-142] (Supplementary Table 3, see Supplementary Material).

Our results confirm the efficacy of pulse CYC in NPSLE, since more than 80% of events demonstrated at least moderate improvement from their baseline status during the follow-up period. Our finding of higher response rates in cases where CYC was given as 1st line therapy could imply that intense immunosuppression is more efficacious if instituted early in NPSLE. Not withstanding the retrospective nature of our data, in cases wherein gonadotoxicity is not a major concern, pulse CYC should not be withheld in severe NPSLE.

The regimen and duration of CYC administration in NPSLE has not been determined. A "treatment paradigm" of remission induction for 6 months and subsequent maintenance therapy has been unambiguously established for lupus nephritis (LN) [143, 144], and a similar approach for NPSLE is practically followed in the two study centres. One of the centres used CYC pulses in some cases, as maintenance therapy; it is of interest that we found no difference in outcome with such prolonged CYC pulses and increased cumulative doses. Our data suggest that a predefined six-month induction period may be sufficient for CYC to exert its therapeutic effects in most cases; thereafter, either maintenance therapy with agents typically used in renal SLE, mainly azathioprine, or "rescue" therapy with RTX in cases of no response seem reasonable options. Prospective and controlled studies to formally test this treatment paradigm are needed.

Evaluation of treatment efficacy in NPSLE is complicated by the absence of validated outcome measures to optimally assess clinical response. Moreover, treatment of several manifestations is often multidirectional, combining immunosuppressive agents, antiplatelets/anticoagulants and symptomatic therapy, thus making it difficult to attribute improvement of symptoms exclusively to a single agent. Although repeat brain magnetic resonance imaging (MRI) has been used to assess response, MRI is often normal or yields nonspecific findings in the initial phase [65], therefore it cannot be considered as a universal monitoring modality [145]. Recurrences of the original

manifestation could represent a practical endpoint at least for some manifestations, and we found reassuringly low relapse rates in our cohort.

Long-term high-dose CYC therapy has been associated with side effects such as gonadal toxicity, infectious complications and malignancies [146]. Route of administration and cumulative dose are the driving determinants of the drug's tumorigenicity (mainly urinary tract and possibly hematological cancers) [147], with data suggesting a total dose of less than 30 gr to be associated with low risk for bladder malignancy [147]; accordingly, we did not document neoplasias in our cohort after a median 4-year follow-up. The age group of lupus patients confers the additional problem of potential gonadal toxicity of CYC. An older pilot study of young women treated with IV CYC for lupus nephritis showed that addition of a depot GnRH agonist reduced occurrence of amenorrhea from 30% to 5% [148]. In our study, gonadal protection during CYC administration in women younger than 45 was routinely implemented in one of the study centres (Heraklion). The three patients that developed premature gonadal failure had not received protection due to non-establishment of such a routine protocol in Cluj.

Several limitations of our study have to be acknowledged. Its retrospective and uncontrolled design with the lack of a control patient group precludes the extraction of firm conclusions regarding efficacy. The arbitrary scale we used to assess outcome is intrinsically subjective and the fact that all patients were not treated in the same centre may have led to bias. A hard and meaningful endpoint to assess NPSLE outcome is still an unmet need in the field. Regarding safety, duration of follow-up in our cohorts was variable, with a median of approximately 5 years. Accordingly, one cannot exclude adverse events occurring at a later stage of follow-up. Additionally, amenorrhea by self-report is not the ideal means to detect ovarian failure, which additionally necessitates serum measurement of follicle-stimulating hormone (FSH) and/or anti-Müllerian hormone levels.

In conclusion, herein we report the long-term efficacy and safety of CYC in the largest to date case series of SLE patients with inflammatory neuropsychiatric manifestations. Until more robust data are available and novel agents are tested in everyday clinical practice, CYC will remain a fundamental therapeutic option for severe cases of NPSLE.

5.1 Characterization of SLE patients with demyelinating features - Coexistence of SLE and MS

We found that coexistence of the two disorders reaches an estimated point prevalence of about 1% among patients with SLE or MS. These patients tend to have mild SLE without major extra-CNS organ involvement, which does not require intensive immunosuppressive treatment. MS tends to follow a relapsing-remitting course (frequent relapses), yet with minimal accumulation of disability and its clinical severity dictates the choice of immunomodulating agents.

The diagnosis of clinically definite MS was established according to the revised McDonald criteria [97]. Traditionally, diagnosis of MS necessitates dissemination of symptoms in space and time, which could take months or years before being established with certainty. To improve sensitivity and allow for earlier MS diagnosis, especially in the case of a clinically isolated syndrome, the 2010 revision of the McDonald criteria simplified interpretation of MRI, so that DIS and DIT can be established from a single brain MRI scan [97]. In the past, the term "lupoid sclerosis" was coined to describe SLE patients with complex neurologic deficits similar to those seen in MS [98]. However, its vague definition was a source of confusion and hence it has now practically been abandoned. The ACR has instead introduced the term "demyelinating syndrome", with diagnostic criteria closely resembling those of definite MS which include symptomatic CNS WM lesions, transverse myelopathy, optic neuropathy, diplopia due to nerve palsies or internuclear ophthalmoplegia and brain stem disease, each occurring at a different time point [21]. By using the ACR definition of demyelinating syndrome, the latter is considered a rare manifestation of NPSLE (cumulative incidence ~ 0.3% of SLE patients)[17, 32]. Indeed, recent cohorts of NPSLE patients from different countries have confirmed very low prevalence rates, ranging from 0 - 1.9% of all NPSLE manifestations[22, 23, 37, 69]. Similarly, we found no patients fulfilling the criteria for this definition and, in fact, NPSLE was excluded in our case series based on fulfillment of the McDonald criteria for definite MS and the absence of any other SLE-related neuropsychiatric manifestations in all patients. It is thus prudent to say that SLE patients presenting with such features should be closely followed-up to rule in or out the possibility of coexisting MS.

Although more than one autoimmune diseases may aggregate in a particular individual, coexistence of MS and SLE has only rarely been reported. Population-based nationwide studies from various regions have identified MS patients who are diagnosed with additional inflammatory and autoimmune diseases including SLE [78 cases in a total of nearly 22,000 patients with MS (0.3%)] [149-153]. Interestingly, a recent meta-analysis found a trend for increased risk of SLE in patients with MS (odds ratio 2.80, 95% confidence interval 0.76 to 10.25), although this association did not reach statistical significance (p=0.12) and there was a significant heterogeneity between studies [154]. Our finding of a higher frequency of SLE/MS coexistence in our cohorts (over 1%) should be interpreted with caution, since our institution is a tertiary referral center for cases with possible SLE or MS.

Indeed, accounting for the total population of Crete (623,065 according to 2011 census), the observed prevalence of SLE/MS coexistence approximates 0.001%, which agrees with the combined probability for having both diseases (108 per 10^5 and 100 per 10^5 for MS and SLE, respectively) [114].

Both SLE and MS are considered to develop as a consequence of environmental factors posed upon individuals with a susceptible genetic background. Novel high-throughput technologies have substantially expanded existing knowledge regarding genetics of complex diseases such as these. Genome wide association studies (GWAS) have confirmed that, apart from loci within the major histocompatibility complex (MHC) which confer the greater risk, multiple non-MHC genes mainly involved in the regulation of immune responses also account for heritability of both SLE and MS [155, 156]. In this regard, it is noteworthy that while a lot of the identified autoimmunity loci seem to be shared among multiple autoimmune diseases [157], recent studies suggest that only a limited genetic overlap exists between lupus and other autoimmune diseases, including MS [158]; this implicates that SLE may have a relatively unique non-MHC genetic susceptibility, certainly distinct from MS. At gene expression level, high-throughput microarray techniques have provided substantial insight into the underlying mechanisms of the two diseases. An initial microarray study showed that genes involved in apoptosis, cell cycle, inflammation and regulation of matrix metalloproteinase proteins are upregulated in both SLE and MS, implicating common pathways [159]. However, subsequent elegant studies have uncovered discrete transcriptome signatures, which include interferon signaling and granulopoiesis in SLE [160, 161], as compared to a robust T-cell activation/proliferation in MS [162]. Table 5.1 summarizes common and distinct genomics and transcriptomics between SLE and MS, along with the cellular functions in which the identified genes are implicated.

A cardinal difference between SLE and MS is the putative role of type I interferons (IFNs) in disease pathogenesis. As stated above, a type I IFN signature is eminent in SLE and peripheral blood mononuclear cells (PBMCs) from active SLE exhibit upregulation of multiple IFN-inducible genes [160]. *In vivo* disruption of the type I IFN pathway has been shown to protect lupus-prone mice from disease development [163]. On the contrary, IFN-β (a type I IFN) constitutes a fundamental treatment option in MS, although the precise mechanism of action remains elusive [164]. While IFN-β administration has been associated with the development of lupus [165], here we observed no flares in patients who received IFN after SLE had been diagnosed. Interestingly, a similarly increased risk for relapses has been observed after IFN administration for treatment of NMO [166]. This observation has led to the hypothesis that SLE may share more features with NMO than with MS; indeed, a significant proportion (44%) of patients with NMO seem to carry ANA [167], while several reports have described occurrence of NMO-spectrum disorders in SLE patients [168]. To this end, serum type I IFN activity and IFN-β– induced responses in PBMCs *in vitro* were found similarly high in SLE and NMO patients, contrasting the low activity in MS patients [169]. Although preliminary, these findings

Table 5.1 Genetic and transcriptomic similarities and discrepancies between SLE and MS, as revealed by novel, high-throughput techniques

Genetic susceptibility	Gene expression
Shared between SLE and MS	
SH2B3 (Negative regulator of T-cell receptor signaling)	TRAF5, CASP8 (Apoptosis)
IL12A (T- and NK cell activation)	CTBP1 (Cell cycle)
RPL19P8 (Pseudo-gene)	IL11RA, CD19 (Inflammation)
CD40 (Activation of DCs, B-cells and macrophages)	TIMP, TGIF, IL1β, VEGF (Regulation of matrix metalloproteinase pathway)
IRF8 (Interferon signaling)	
SLE specific	
Dendritic cell function and IFN signaling	Interferon signaling
IRF5, STAT4, SPP1, IRAK1	IFI35, IFIT1, IFIT3, IFITM1, OAS1
T-cell function and signaling	Granulopoiesis
PTPN22, TNFSF4, PDCD1, IL10	MPO, elastase, F2RPA, defensin3
B-cell function and signaling	Immune response
BANK1, BLK, LYN, BCL6,	CCL3, CCR1, CD163, IL1R2
Immune-complex processing and innate immunity	Protein folding
ITGAM, C1QA, C2, C4A, C4B	SLP1
Cell cycle, apoptosis, and cellular metabolism	
CASP10, NMNAT2, PTTG1, ATG5	
Transcriptional regulation	
JAZF1, UHRF1BP1, BCL6, MECP2	
MS specific	
B-cell function and signaling	T- cell activation and expansion
IL7, IL7R, CD86, CXCR5, VCAM1	LEF1, TCF3, SLAM
T-cell function and signaling	
CBLB, EOMES, IL12B, IL2RA, IL7, IL7R, THEMIS	

provide initial evidence suggesting distinct pathophysiological pathways between diseases with similar clinical phenotype but markedly different response to the same therapy.

The potential presence of aPL antibodies serves to add more complexity in the clinical scenario of the patient presenting with manifestations suggesting NPSLE or MS. Circulating aPL antibodies are not uncommon in MS, although their prevalence varies widely among studies (2–30%) [170, 171]. Conversely, APS may present with a wide variety of neurologic manifestations beyond stroke [103]. In an early study, Cuadrado *et al* examined 27 patients initially labeled as "possible MS" with atypical features (atypical imaging findings or evolution, symptoms suggestive of connective tissue disease), referred to a lupus clinic; all patients tested positive for aPL and actually fulfilled criteria for APS (either primary or secondary) [104]. Notwithstanding the limitation of potential referral bias, this observation led some experts to include APS in the differential diagnosis of MS, especially when the latter presents with atypical findings [105]. In our case series, 2 of 6 patients (33%) indeed carried aPLs at low-to-moderate titers, albeit none qualified for a diagnosis of APS and MRI findings were highly suggestive of demyelination.

In summary, we found that approximately 1% of SLE patients in our well-characterized cohort also fulfill criteria for MS. The coexistence of the two diseases does not seem to be associated with a severe phenotype for either entity although our findings need to be verified in larger, more racially diverse cohorts of patients. The prognosis of these patients, followed by a multidisciplinary group of specialists, is favorable with only slight increase in neurological disability over a 4-year follow-up.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Indications of diagnostic and therapeutic modalities in different neuropsychiatric manifestations according to the EULAR recommendations

	Diagnosis					Therapy		
	Brain MRI	**Spinal MRI**	**CSF analysis**	**NCS**	**EEG**	**Immunosuppression**	**Antiplatelet/Anticoagulation**	**Symptomatic**
CVD	Yes	No	No	No	No	Rarely	No	No
Cognitive disorder	Yes, in case of: age < 60, rapid unexplained or moderate-to-severe cognitive decline, recent and significant head trauma, new onset of other neurological symptoms or signs, development of cognitive dysfunction in the setting of immunosuppressive or antiplatelet/anticoagulation therapy	No	No	No	No	Yes, only to control concurrent SLE or NPSLE activity	No	Yes
Chorea	Yes	No	No	No	No	Yes, when generalized disease activity	Considered when aPL (+)	Yes
Psychosis	Yes, when additional neurological symptoms or signs are present	No	No	No	No	Yes, when generalized disease activity	No	Yes
Mood disorder	No	No	No	No	No	No	No	Yes
Seizure disorder	Yes	No	Yes, to exclude infection	No	Yes	Yes, when generalized disease activity	Considered when aPL (+)	Yes, in refractory cases
Myelopathy	Yes	Yes	Yes	No	No	Yes	Considered when aPL (+)	No

Cranial neuropathy	Yes	No	No	No	No	Yes	Considered when aPL (+)	No
Acute confusional state	Yes	No	Yes	No	No	Yes, in severe cases	No	Yes
Peripheral neuropathy	Yes, when focal neurological signs, gait disturbance, visual or urinary disorder, increased tendon reflexes and/or muscle tone are present		No	Yes	No	Yes	No	No
Mononeuritis multiplex			No	Yes	No	Yes	No	No
Acute demyelinating polyradiculopathy			Yes	Yes	No	Yes	No	No
Plexopathy			No	Yes	No	Yes	No	No
Myasthenia gravis			No	Yes	No	Yes	No	No
Lupus headache	Not specified							
Aseptic meningitis	Not addressed							
Anxiety disorder	Not addressed							
Autonomic disorder	Not addressed							
Demyelinating disorder	Not addressed							

NPSLE: Neuropsychiatric SLE; CVD: Cerebrovascular disease; aPL: Antiphospholipid antibodies; MRI: Magnetic resonance imaging; EEG: Electroencephalogram; CSF: Cerebrospinal fluid; NCS: Nerve conduction studies

Supplementary Table 2. Definitions of response to CYC according to different neuropsychiatric manifestation, as evaluated at last follow-up visit

Manifestation	Complete response	Partial response	Stabilization	Deterioration/therapy fai
Psychosis	Complete resolution of psychotic symptoms (eg. auditory/visual hallucinations) with no relapses (psychiatric evaluation)	Significant improvement but presence of residual symptoms (psychiatric evaluation)	Lack of significant symptomatic improvement (psychiatric evaluation)	Worsening of psychotic features from baseline (psychiatric evaluation)
CVD	**All** of the following: ▪ No CVD relapse ▪ mRS score at last f/u < baseline ▪ mRS score at last f/u ≤ 2	**All** of the following: ▪ No CVD relapse ▪ mRS score at last f/u < baseline ▪ mRS score at last f/u 3 - 4	**All** of the following: ▪ No CVD relapse ▪ mRS score at last f/u = baseline	**One** of the followin ▪ CVD relapse ▪ mRS score at > baseline
Myelopathy	▪ EGS score at last f/u < baseline ▪ mRS score at last f/u ≤ 1	▪ EGS score at last f/u < baseline ▪ mRS score at last f/u ≤ 3	▪ EGS score at last f/u = baseline	▪ EGS score at last f/ baseline
Polyneuropathy	Disappearance of sensory symptoms/signs of involved limbs (neurologic examination ± NCS)	Improvement of sensory symptoms/signs of involved limbs but residual deficits (neurologic examination ± NCS)	Unaltered sensory symptoms/signs of involved limbs from baseline (neurologic examination ± NCS)	Worsening of sensory symptoms/signs of invo limbs from baseline (neurologic examinatior NCS)
Seizures	Absence of new seizures	Decrease in seizure frequency	Unaltered seizure frequency	Increase in seizure frequ
Cranial neuropathy	▪ Optic neuropathy: Normalization of VA (ophthalmologic evaluation) ▪ Sensorineural hearing loss: Normalization of AF (audiogram) ▪ Trigeminal neuropathy: Disappearance of sensory symptoms/signs (neurologic evaluation)	▪ Optic neuropathy: Improvement of VA but residual deficit (ophthalmologic evaluation) ▪ Sensorineural hearing loss: Normalization of AF (audiogram) ▪ Trigeminal neuropathy: Improvement but residual sensory symptoms/signs (neurologic evaluation)	▪ Optic neuropathy: Unaltered VA (ophthalmologic evaluation) ▪ Sensorineural hearing loss: Normalization of AF (audiogram) ▪ Trigeminal neuropathy: Unaltered sensory symptoms/signs (neurologic	▪ Optic neuropathy: Normalization of V (ophthalmologic evaluation) ▪ Sensorineural heari Normalization of A (audiogram) ▪ Trigeminal neuropa Deterioration of ser

			evaluation)	symptoms/signs (neurologic evaluat
Mononeuritis multiplex	Complete restoration of motor function of involved limb (neurologic examination ± NCS)	Improvement of motor function of involved limb but residual deficit (neurologic examination ± NCS)	Unaltered motor function of involved limb from baseline (neurologic examination ± NCS)	Worsening of motor fun of involved limb from b (neurologic examinatior NCS)
Aseptic meningitis	Complete restoration of neurologic symptoms and cognitive function (neurologic examination)	Improvement of neurologic symptoms but residual neurologic deficit (neurologic examination)	NA	ICU admission or death d severe neurologic deficit or complications
Headache	Complete resolution of headache	Improvement of pain intensity > 2 in a 0-10 pain scale	No change in pain intensity in a 0-10 pain scale	Worsening of pain inte a 0-10 pain scale
Acute confusional state	Complete restoration of higher-order thinking and general cognitive function (clinical examination)	Incomplete but significant restoration of higher-order thinking and general cognitive function (clinical examination)	Unaltered cognitive function from baseline (clinical examination)	One of: stupor, coma, de
Acute demyelinating polyradiculopathy	Complete restoration of lower limb motor function (neurologic examination ± NCS)	Partial restoration of lower limb motor function - normal walking (neurologic examination ± NCS)	Unaltered motor function from baseline (neurologic examination ± NCS)	Worsening of motor f from baseline, p (neurologic examinat NCS)
Mood disorder	Complete recovery from depressive symptoms - patient not fulfilling criteria for major depression (psychiatric evaluation)	Partial improvement of depressive symptoms (psychiatric evaluation)	Unaltered mood from baseline (psychiatric evaluation)	Deterioration of mood f baseline (psychiatric evaluation)
Cognitive disorder	No cognitive deficit (neuropsychological assessment)	Improvement in cognitive performance from baseline but residual deficit (neuropsychological assessment)	Unaltered cognitive performance from baseline (neuropsychological assessment)	Deterioration of cognitiv performance from basel (neuropsychological assessment)

[a] For all manifestations, escalation of immunosuppressive treatment (eg. with rituximab) was by definition considered as a treatment failure - CVD: Cerebrovascular disease; f/u: Follow-up; mRS: Modified Rankin scale; EGS: Edmus grading scale; NCS: Nerve conduction studies; VA: Visual acuity; AF: Auditory function; NA: Not applicable; ICU: Intensive care unit

Supplementary Table 3. Summary of studies evaluating efficacy and safety of cyclophosphamide in neuropsychiatric SLE

Author	Type of study	Number of patients Months of follow-up	Protocol	Line of CYC therapy	Favorable outcome	Relapse	Adverse events
Boumpas *et al* [138]	Observational	9 51 (20-140)	CYC IV: 0.75-1g/m^2 BSA	1st line: 45%	100%	0%	Herpes zoster: 1 Severe infections: 1 Deaths: sepsis 1
Neuwelt *et al* [140]	Observational	31 NK	CYC IV: 0.25-0.5g/m^2 BSA (n=11) 0.5-1g/m^2 BSA(n=20)	1st line: 10%	61%	NK	Deaths: sepsis 2, malignancy 1
Ramos *et al* [141]	Observational	15 NK	IV CYC: 500mg weekly at least 3 weeks, then monthly	1st line: 68%	93%	26.6%	Infections: 2
Baca *et al* [136]	Observational Pediatric	7 37(8-55)	CYC IV: 0.5g/m^2 BSA monthly for 3 months, the every 2-3 months	1st line: 100%	100%	0%	(-)
Mok *et al* [172]	Observational	13 86 (21-169)	CYC oral: 1-2mg/kg/day 6 months, then AZA 1-2mg/kg/day	1st line: 100%	100%	7.7%	Herpes zoster: 5 Transient amenorrhea: 3
Stojanovich *et al* [142]	Controlled trial	60 (37 CYC vs. 23 GC) NK	CYC IV: 200-400mg/month Vs. Prednisone oral (20.5mg/day)	1st line: 100%	CYC: 62.2% vs. GC: 21.7%	CYC: 38% Vs. GC: 78%	Herpes zoster: 2
Barile-Fabris *et al* [135]	Randomized controlled trial	32 (19 CYC vs. 13 MP) NK	CYC IV: 0.75g/m^2 BSA monthly for 1 year, then at 3 months for another year vs MP: Monthly for 4 months, then 2 x every 2 months, then 4x every 3 months	1st line: 100%	CYC: 95% MP: 46%	Relapses in the MP arm	CYC: herpes zoster 2, Infections 16 MP: Pancreatitis 1, Uncontrolled hypertension 1, Infections 12
Martin-Suarez *et al* [139]	Observational	10	CYC IV: 500mg weekly 3 (2-10) weeks, then AZA 2g/kg/day vs. CYC 500mg monthly	1st line: 70%	NPSLE: 80%	NPLES: NK LES: 32%	Herpes zoster 3 Sepsis 2 Infections 1 Hemorrhagic cystitis 3 Transient amenorrhea 4

BSA, body surface area; CYC, cyclophosphamide; IV, intravenous; MP, methylprednisolone; GC, glucocorticoids; AZA, azathioprine; NPSLE, neuropsychiatric lupus; NK, not done or not reported

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EULAR recommendations for neuropsychiatric systemic lupus erythematosus *vs* usual care: results from two European centres

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Abstract

Objective. To compare the European League Against Rheumatism (EULAR) recommendations for the management of NPSLE with usual care in two tertiary centres and to detect potential pitfalls in their use for diagnosis and treatment.

Methods. A chart-based review of NPSLE manifestations was conducted in two European centres. Diagnostic and treatment decisions were compared against the EULAR recommendations for general NPSLE and specific manifestations.

Results. We studied a total of 94 patients who experienced 123 lupus-related neuropsychiatric events over 10 years. In 80% of the events, at least one EULAR-defined risk factor (previous NPSLE, generalized disease activity or aPL positivity) was present. Overall, there was good concordance between clinical care and recommendations for diagnosis and treatment (68.7% and 62.7% of events, respectively). Brain MRI was performed in the absence of a clear EULAR recommendation in 42.9% of events; therein, it was more frequently normal compared with imaging performed according to the recommendations (52.4% *vs* 18.5%, $P = 0.008$), and it did not influence management. Among patients reporting cognitive dysfunction, only 27.8% underwent the recommended neuropsychological assessment. In line with the recommendations, immunosuppressants were more frequently given in events suggestive of an inflammatory process (80.5% *vs* 47.6% in non-inflammatory events, $P < 0.001$). Notably, 52% of cerebrovascular events were managed with combined immunosuppressive/antithrombotic therapy due to either coexisting generalized lupus activity or recurrence despite prior antithrombotic treatment.

Conclusion. Despite good concordance between EULAR recommendations for NPSLE and usual clinical practice, we identified a number of issues (such as overutilization of brain MRI, suboptimal evaluation of cognitive dysfunction, and frequent use of immunosuppressives in cerebrovascular disease) that need to be investigated further.

Key words: neuropsychiatric SLE, EULAR recommendations, MRI, immunosuppressive therapy.

Rheumatology key messages:

- In tertiary centres, there is good (>60%) agreement between usual care and the EULAR neuropsychiatric SLE recommendations.
- In NPSLE, brain MRI is more often informative when performed according to the EULAR recommendations
- More than 60% of patients experiencing cerebrovascular disease have generalized lupus activity.

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Introduction

Patients with SLE may experience a variety of neurological and psychiatric manifestations, collectively named NPSLE, that account for significant morbidity and mortality [1]. The prevalence of NPSLE varies widely, from 21% to 95% in various cohorts [2, 3], in part due to the heterogeneity of manifestations and definitions used [4]. In NPSLE, attribution of neuropsychiatric events to lupus warrants a thorough investigation and exclusion of alternative causes. Indeed, primary NPSLE (events directly attributed to the disease) constitutes <40% of all cases [5, 6]. The remaining cases may be caused by complications of the disease or its therapy (secondary NPSLE), or may be unrelated to SLE and be due to infections, metabolic abnormalities and adverse drug reactions. In primary NPSLE, direct neuronal injury due to autoantibodies against *N*-methyl-D-aspartate glutamate receptor (anti-NR2), accelerated atherosclerosis and thrombotic diathesis caused by the presence of aPL are considered potential pathogenic mechanisms [7].

Notwithstanding the significant advances in our understanding of its pathogenesis, NPSLE continues to pose considerable diagnostic and therapeutic challenges. Diagnostic workup and treatment decisions are typically performed on a patient-by-patient basis and often necessitate the involvement of multiple medical specialties. In an effort to homogenize the management of patients with NPSLE, a European League Agaisnst Rheumatism (EULAR) task force has issued a set of recommendations, addressing diagnostic and therapeutic issues using a combination of evidence-based approach and expert consensus [8]. The recommendations cover both general NPSLE and specific NPSLE disorders, identify risk factors for its occurrence, and provide evidence on the value of diagnostic modalities and therapeutic options. In view of the former considerations, we sought to compare the EULAR recommendations against usual clinical care of NPSLE patients in two tertiary hospital centres, in an attempt to detect potential limitations in their use for diagnosis and therapy.

Patients and methods

Study population

Two national tertiary referral centres for patients with SLE and suspected neuropsychiatric involvement, Heraklion (Greece) and Cluj (Romania) participated in the study. The study was approved by the Institutional Review Board of the University Hospital of Heraklion (Greece) and that of the Iuliu Hatieganu University of Medicine and Pharmacy in Cluj (Romania). A consent form was not obtained because of the retrospective, observational nature of the study. Patients with confirmed neuropsychiatric involvement were selected (by retrospective chart review) from 650 lupus cases over the last decade (2001–12). All patients fulfilled at least four of the revised ACR classification criteria for SLE [9] at the time of NPSLE diagnosis and had undergone regular follow-up in each centre.

For each neuropsychiatric manifestation included in our study, we recorded all diagnostic procedures undergone by the patients, together with the therapies they received. The following variables were also documented: age, gender, ethnicity, smoking and cardiovascular risk factors, disease duration, presence of aPL, history of previous major organ involvement, and medication history. Disease activity and damage at the time of neuropsychiatric event were cross-sectionally assessed with the Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA)-SLEDAI [10] and the SLICC/ACR Damage Index, respectively [11]. Time lag between diagnosis of SLE and occurrence of NPSLE was calculated in years.

The presence of generalized disease activity at the time of the neuropsychiatric event was defined as follows. First, a SELENA-SLEDAI $\geqslant 4$ after exclusion of the neuropsychiatric components (non-neuropsychiatric SELENA-SLEDAI). Although not a formally validated index for disease activity, we used the non-neuropsychiatric SELENA-SLEDAI to capture extra-neuropsychiatric disease activity. The cut-off value of $\geqslant 4$ was chosen based on data showing that total SLEDAI (SLEDAI-2 K version) scores above 3 or 4 may be more appropriate for defining active disease associated with intensification of immunosuppressive therapy [12]. Second, in the case of non-neuropsychiatric SELENA-SLEDAI <4, if the physician global assessment of disease status (as incorporated in the SELENA-SLEDAI form) was $\geqslant 2$, this was indicative of at least medium disease activity [10]. This cut-off value of physician global assessment has been used in previous observational studies to denote severe disease in SLE [13].

Neuropsychiatric events, work-up and outcome

Neuropsychiatric events were defined according to the ACR nomenclature and case definitions [14]. For patients experiencing more than one neuropsychiatric event, each event was registered individually. The attribution of neuropsychiatric syndromes to SLE was based on physician judgement and was made by the treating physician with the help of experts from different disciplines including: internal medicine, infectious diseases, neurology, psychiatry, and neuroimaging. Attribution to SLE was reached following fulfilment of the following criteria: diagnosis of SLE (ACR criteria); presence of neuropsychiatric manifestation included in the ACR nomenclature for NPSLE; absence of another diagnosis that could potentially explain symptoms, according to exclusion and association factors of the ACR nomenclature [14]. Alternative diagnoses included, but were not limited to: CNS infections, metabolic abnormalities, and adverse drug reactions. Following their exclusion, only events directly attributed to lupus were included in the study.

The standard neuroimaging procedure for NPSLE in both centres is the EULAR-recommended brain/spinal cord MRI protocol, which includes conventional MRI

sequences (T1/T2, FLAIR), diffusion-weighted imaging (DWI) and gadolinium-enhanced T1 sequence. Brain MRIs were interpreted by confirmed neuroradiologists in each centre (both referral centres for NPSLE) as part of the standard approach to diagnosing possible NPSLE. Abnormalities (including white and grey matter hyperintensities, cerebral infarcts, intracranial haemorrhages, cerebral venous thromboses and brain atrophy) were recorded. MRI results were classified as either diagnosis specific when findings were diagnostic of a specific neuropsychiatric entity, or diagnosis non-specific (useful for exclusion of other causes in all other cases). Due to the heterogeneity of manifestations, the outcome of neuropsychiatric events at 6 months was evaluated according to an arbitrary 3-level categorical outcome as improved, stable or worse.

Comparison of clinical care with the EULAR statements and recommendations

The EULAR recommendations comprise a total of 27 statements addressing both the general approach to NPSLE and individual neuropsychiatric syndromes [8]. To calculate concordance rates between clinical practice and the recommendations, we extracted these 27 statements and scrutinized the manuscript text for additional recommendations not included in the statements. Next, we compared the diagnostic and therapeutic decisions applied in each registered neuropsychiatric event against the EULAR recommendations (both the general ones and those specific to the event). In calculation of concordance rates we excluded cases of lupus headache, autonomic disorder, and anxiety disorder (18 cases total; all defined according to ACR case definitions [14]), since the optimal work-up and treatment for these manifestations is not discussed in the recommendations.

Since the EULAR recommendations were published in 2010, our study period largely reflected usual care prior to their publication. To assess their potential impact on the management of NPSLE, we performed a *post hoc* analysis to compare agreement between usual care and recommendations relative to the time of NPSLE occurrence (prior to *vs* after 2010).

Statistical analysis

Data analysis was performed with IBM SPSS Statistics (version 21.0). Descriptive statistics were undertaken for continuous variables, and median values with interquartile ranges (IQR) were calculated. Chi-squared or Fisher's exact test was used to compare categorical variables, and the non-parametric Mann–Whitney *U*-test was used to compare continuous variables. Statistical significance was indicated by a two-sided $P < 0.05$.

Results

Patients and neuropsychiatric events

We identified 94 patients who had experienced a total of 123 lupus-related neuropsychiatric events ($n = 71$ patients with a single event, $n = 17$ with two events, $n = 6$ with three events) (Table 1). At the time of the neuropsychiatric event, at least one of the EULAR-defined risk factors for primary NPSLE (previous NPSLE, generalized disease activity, and aPL positivity) was present in almost 80% of events. Approximately 35% of events occurred within the first year after SLE diagnosis (26% as presenting manifestation of the disease).

Neuropsychiatric events and accompanying clinical characteristics (aPL status, SLE activity, and damage at the time of NPSLE occurrence) are listed in supplementary Table S1, available at *Rheumatology* Online. The most prevalent events were cerebrovascular disease (CVD) ($n = 21$, 17.1%), cognitive dysfunction ($n = 18$, 14.6%), intractable lupus headache and mood disorder ($n = 12$ each, 9.8%), seizure disorder and transverse myelitis ($n = 11$ each, 8.9%). Manifestations (excluding those with fewer than five registered cases) accompanied by the highest generalized (non-neuropsychiatric) disease activity were psychosis and cognitive disorder, followed by myelopathy and CVD.

Brain MRI was performed in 75 neuropsychiatric events (61.0% of total events). In 21 of them (28.0%), MRI was considered normal; in the remaining cases, the most common finding was non-specific periventricular white matter hyperintensities (WMHIs, 40.8% of events), followed by cerebral infarcts (21.1%). Other diagnostic procedures included cerebrospinal fluid (CSF) analysis in 25 events, nerve conduction studies (NCS) in 14, and electroencephalogram in 8 events.

Treatment of NPSLE included steroids (either initiation or escalation of previous dose) in 89 events (72.4%), and immunosuppressants in 73 events (59.3%). The latter included i.v. CYC (42 cases), AZA (22 cases) and rituximab (5 cases). Antithrombotic therapy was administered in 41 neuropsychiatric events (anti-platelet agents in 30 and vitamin K antagonists in 11 cases), most commonly in ischaemic CVD (supplementary Table S2, available at *Rheumatology* Online).

In the majority of cases, the short-term outcome of NPSLE was favourable, with 96 events (78%) showing at least mild improvement and 22 (17.9%) remaining stable at 6 months. Manifestations with the most favourable course were psychosis, seizure disorder (the majority having resolved within 6 months) and transverse myelopathy (supplementary Table S2, available at *Rheumatology* Online).

Comparison of routine care with the EULAR recommendations

In Table 2 we compare the EULAR recommendations (diagnosis and therapy) with the clinical care followed in the registered NPSLE cases. No statistically significant differences were observed between the two study centres. In addition, we did not observe statistically significant differences (in terms of agreement with the EULAR recommendations) when neuropsychiatric events were stratified according to the time they occurred (prior to or after 2010, year of publication of the EULAR recommendations) (Table 3).

Table 1 Demographic and clinical characteristics of 94 patients and 123 neuropsychiatric events

Characteristic	Value
Female, *n* (%)	84 (89.4)
Nationality, *n* (%)	
Greek	48 (51.1)
Romanian	46 (48.9)
Age at SLE onset, median (IQR), years	37.0 (23.0)
Age at NPSLE, median (IQR), years	42.0 (16.5)
Time lag between SLE onset and NPSLE occurrence, median (IQR), years	4.0 (7.0)
NPSLE risk factors	
Generalized disease activity at neuropsychiatric event, *n* (%)	76 (61.8)
aPL (+) at neuropsychiatric event, *n* (%)	43 (35.0)
Previous severe neuropsychiatric event, *n* (%)	30 (24.4)
Any risk factor	96 (78.0)
SLEDAI at neuropsychiatric event, median (IQR)	8.0 (10.0)
Concomitant disease activity at neuropsychiatric event, *n* (%)	
Mucocutaneous domain	53 (68.8)
Musculoskeletal domain	51 (62.2)
Renal domain	16 (20.8)
Haematological domain	23 (29.9)
SDI at neuropsychiatric event, median (IQR)	0.0 (1.0)
Medication received at the time of neuropsychiatric event, *n* (%)	
HCQ	58 (47.2)[a]
AZA	28 (22.8)
MTX	8 (6.5)
MMF	5 (4.1)
CYC	3 (2.4)
Ciclosporin	2 (1.6)
Aspirin	24 (19.5)

[a]Of the remaining 65 events wherein patients were not receiving HCQ, in 32/65 (49.2%) the neuropsychiatric event was the presenting manifestation. The remaining 33/65 (50.8%) were due to non-compliance, thus contributing to the overall low frequency of HCQ use.

Diagnostic work-up

The EULAR recommendations advocate the use of brain MRI in CVD, seizures, chorea, and acute confusional state (ACS), and also in selected cases of cognitive dysfunction, myelopathy and psychosis (supplementary Table S3, available at *Rheumatology* Online). Brain imaging was performed in 54 of 74 (73.0%) events in which it was recommended, as compared with 21 of 49 (42.9%) events in which it was not recommended ($P = 0.01$). Notably, in the latter cases brain MRI was more likely to reveal no abnormalities [11/21 (52.4%) *vs* 10/54 (18.5%), considered normal $P = 0.008$]. MRI was considered specific for diagnosis only in cases of CVD and also in two cases of cranial neuropathy (V and VII, one each). In all other cases, MRIs were considered non-specific or useful for exclusion of other causes (infections, etc.) for the neuropsychiatric syndrome (supplementary Table S2, available at *Rheumatology* Online). The presence of non-specific WMHIs spanned the whole spectrum of neuropsychiatric events, irrespective of the indication for MRI ($P = 0.80$).

CSF analysis is specifically recommended by EULAR in cases of ACS, aseptic meningitis, myelopathy and inflammatory demyelinating polyradiculopathy, and it was carried out in 11 of 15 (73.3%) such events. However, lumbar puncture was also performed in cases without clear recommendation, albeit less frequently [14/96 (14.6%) events, $P < 0.001$]. These were cases of cranial neuropathy, psychosis, mood disorder and cognitive disorder. On all occasions, CSF analysis was performed to exclude alternative diagnoses, particularly infection; findings were suggestive of NPSLE, albeit non-specific in all cases (pleocytosis and/or increased protein), with the exception of a single case of acute demyelinating polyradiculopathy, in which results were typical (elevated protein with the absence of pleocytosis).

Electroencephalogram and NCS were generally undertaken in accordance with the recommendations [8/11 cases of seizures and 8/8 of peripheral neuropathy, respectively). NCS were also performed in more than half of myelopathy cases (6/11) to exclude alternative diagnoses, although this is not explicitly recommended.

Only 27.8% of patients (5/18) with cognitive dysfunction underwent the formal neuropsychological assessment recommended by EULAR [either the 1-h ACR battery or the computer-based automated neuropsychological assessment metrics (ANAM) system], due to lack of availability of neuropsychologists or time constraints. In the

Table 2 Concordance of clinical practice with the EULAR statements and recommendations

EULAR recommendations	Routine clinical practice, *n* (%)
General approach to NPSLE	
The recommended MRI protocol (brain and spinal cord) includes conventional MRI sequences (T1/T2, FLAIR), DWI and gadolinium-enhanced T1 sequences	Performed in 76 events (61.8) Diagnosis specific only in CVD and cranial neuropathy
Glucocorticoids and immunosuppressive therapy are indicated for neuropsychiatric manifestations felt to reflect an immune/inflammatory process (e.g. ACS, aseptic meningitis, myelitis, cranial and peripheral neuropathies and psychosis) following exclusions of non-SLE-related causes	33/41 (80.5) of inflammatory events received immunosuppressive therapy [*vs* 39/82 (47.6) non-inflammatory, $P < 0.001$]
Anti-platelet/anti-coagulation therapy is indicated when manifestations are related to aPL, particularly in thrombotic CVD[a]	9/12 (75) aPL (+) patients with such manifestations received anti-platelet/anti-coagulation [*vs* 32/111 (28.8) in remaining events, $P = 0.002$]
The use of symptomatic therapies (e.g. anti-convulsants, anti-depressants) and the treatment of aggravating factors (e.g. infection, hypertension and metabolic abnormalities) should also be considered	Implemented in the vast majority: psychosis: 10/10 (100) received antipsychotics; seizures: 10/11 (90.9) anti-convulsants; mood disorder: 12/12 (100) anti-depressants; anxiety disorder: 4/5 (80) anxiolytics
Anti-platelet agents may be considered for primary prevention in SLE patients with persistently positive, moderate or high, aPL titres	7/31 (22.6) aPL (+) patients were receiving anti-platelets prior to NPSLE
CVD	
Atherosclerotic/thrombotic/embolic CVD is common, haemorrhagic stroke is rare and stroke caused by vasculitis is very rare in SLE patients; accordingly, immunosuppressive therapy is rarely indicated	11/21 (52.4) of patients received immunosuppressive therapy
Long-term anti-coagulation should be considered in patients with stroke who fulfil the classification criteria for APS for secondary prevention of recurrent stroke, which commonly occurs	7/11 (63.7) of aPL (+) patients with CVD received long-term anti-coagulation
Cognitive dysfunction	
Severe cognitive impairment. Should be confirmed by neuropsychological tests in collaboration with a clinical neuropsychologist when available	5/18 (27.8) underwent formal neurocognitive assessment to evaluate cognitive function
Management of both SLE- and non-SLE-associated factors as well as psycho-educational support may prevent further deterioration of cognitive dysfunction	0/18 (0) received psycho-educational support
Seizures	
The diagnostic work-up aims to exclude structural brain disease and inflammatory or metabolic conditions and includes MRI and EEG	MRI was performed in 8/11 (72.8): diagnosis non-specific in all cases; EEG was performed in 8/11 (72.8): epileptiform changes in 3, normal in 5 cases
In the absence of MRI lesions related to seizures and definite epileptic abnormalities on EEG following recovery from the seizure, withholding of AED after a single seizure should be considered. Long-term anti-epileptic therapy may be considered for recurrent seizures	10/11 (90.9) received long-term anti-epileptic drugs due to recurrent seizures or epileptiform EEG changes
For most patients without generalized disease activity, immunosuppressive therapy is not indicated for prevention of recurrences or control of refractory seizures	3/6 (50) received immunosuppressive therapy to prevent recurrent seizures, despite the absence of generalized disease activity
Anti-coagulation may be considered in patients with aPL	0/2 received anticoagulation (2/2 received anti-platelet therapy)
Mood disorder/psychosis	
There is no strong evidence to support the diagnostic utility of serological markers or brain imaging in major depression	4/12 (33.3) underwent brain MRI: diagnosis non-specific in all cases
Glucocorticoids and immunosuppressive therapy may be considered in SLE-associated psychosis, especially in presence of generalized disease activity	7/10 (70) patients with psychosis received immunosuppressive therapy
Myelopathy	
The diagnostic work-up includes gadolinium-enhanced MRI and CSF analysis	Spinal MRI was performed and was diagnostic in 10/11 (90.9) and CSF analysis in 8/11 (72.8)
Timely (as soon as possible) induction therapy with high-dose glucocorticoids followed by i.v. CYC should be instituted	High-dose steroids were administered 11/11 (100) and IV CYC in 7/11 (63.7). Rituximab was administered in another 3/11 (27.3)
Peripheral neuropathy/mononeuritis multiplex	
Peripheral neuropathy often co-exists with other neuropsychiatric manifestations and is diagnosed with electromyography and NCS	1/8 (12.5) co-existed with other neuropsychiatric manifestation (cognitive disorder)—8/8 (100) were diagnosed with EEG and NCS
Combination therapy with glucocorticoids and immunosuppressive agents may be considered in severe cases	7/8 (87.5) received immunosuppressive therapy (5 CYC, 1 AZA, 1 ciclosporin)

For specific manifestations, applied in those with $\geqslant$8 events.[a]Apart from thrombotic CVD, these manifestations include chorea, ischaemic optic neuropathy and refractory myelopathy (EULAR recommendations manuscript). CVD: cerebrovascular disease; ACS: acute confusional state; EEG: electroencephalogram; AEDs: anti-epileptic drugs; CSF: cerebrospinal fluid; NCS: nerve conduction studies.

Table 3 Concordance of usual care with the EULAR recommendations for NPSLE stratified according to the timing of neuropsychiatric events

	Level of agreement, *n* (%)			
	Total study period (*n* = 105 events[a])	Period 2001–10[b] (*n* = 76 events)	Period 2011–12[b] (*n* = 29 events)	*P*-value[c]
Diagnostic work-up	103/150[4] (68.7)	68/104 (65.4)	35/46 (76.1)	0.25
Treatment decisions	89/142 (62.7)	64/100 (64)	25/42 (59.5)	0.70

[a]Concordance rates calculated for a total of 105 events. Cases of lupus headache, autonomic neuropathy, and anxiety disorder were excluded due to lack of detailed guidelines for diagnosis and treatment in the EULAR recommendations. [b]EULAR recommendations for NPSLE were published in 2010. [c]Comparison of agreement rates between the 2001–10 and 2011–12 periods. [d]Denominators in the table indicate the total number of diagnostic or therapeutic interventions recommended by EULAR for all neuropsychiatric events included in the study. See also supplementary Table S3, available at *Rheumatology* Online for more details.

remaining cases, diagnosis was made with the Montreal Cognitive Assessment tool (MoCA), a one-page, performance-based questionnaire developed to identify cognitive impairment [15], and was attributed to SLE after the exclusion of alternative causes [median (IQR) MoCA score 20.0 (6.5), indicative of moderate dysfunction).

Therapy

In accordance with the EULAR recommendations, immunosuppressants were administered more frequently in manifestations felt to reflect an immune/inflammatory process, namely ACS, aseptic meningitis, myelitis and cranial and peripheral neuropathies and psychosis (80.5% *vs* 47.6% in non-inflammatory events, $P < 0.001$). Likewise, anti-platelet or anti-coagulation therapies were instituted for events occurring in the presence of aPLs and are thought to be related to the latter, particularly ischaemic CVD, but also chorea, ischaemic optic neuropathy and myelopathy refractory to immunosuppression (75% *vs* 28.8% in events not considered to be related to aPLs, $P = 0.002$) (Table 2).

Regarding CVD in particular, anti-platelet or anti-coagulation was instituted in all 21 cases, with anti-coagulation being reserved for patients fulfilling criteria for APS (7/11 of such cases received vitamin K antagonists). Interestingly, in more than half of CVD events (11/21, 52.4%), physician judgement advocated for the adjunctive use of immunosuppressive treatment; seven patients were treated with CYC, four with AZA and one patient was treated sequentially with AZA, CYC and finally rituximab due to ongoing disease activity and the severity of CVD. To further explore this finding, we assessed levels of disease activity at the time of stroke. A total of 13 of 21 (61.9%) CVD events occurred in the presence of generalized disease activity, and immunosuppressive therapy was instituted in 9/13 (69.2%); major drivers of disease activity were mucocutaneous manifestations (8/13 events), arthritis (7/13), cytopenias (4/13), nephritis (3/13) and serological abnormalities (high anti-dsDNA titre and/or low serum C3/C4) (6/13 events). No significant differences were found regarding patient age and presence of traditional cardiovascular risk factors (smoking, diabetes, hypertension, dyslipidaemia) between CVD events occurring in the presence or the absence of generalized disease activity (data not shown). The remaining two cases treated with immunosuppressants had low-level or no extra-CNS disease activity but suffered from CVD recurrence despite prior antithrombotic treatment. Median [interquartile range (IQR)] non-neuropsychiatric SLEDAI at the time of stroke was significantly higher in cases that received immunosuppression compared with those that did not [6.0 (7.0) *vs* 2.0 (4.0), respectively, $P = 0.04$]. All patients (11/11, 100%) who received combined immunosuppression/antithrombotic treatment, and 8/9 (88.9%) of those who received antithrombotic treatment alone had a favourable outcome at 6 months ($P = 0.30$). In the two cases treated with immunosuppression due to CVD recurrence, no new recurrence was observed at 6 months.

Similarly to diagnosis, the management of SLE patients with cognitive dysfunction was also not in accordance with the EULAR recommendations. Thus, none of the patients underwent psycho-educational interventions (cognitive rehabilitation), and the management of concomitant anxiety and depression was only rarely addressed (Table 2). Nonetheless, at 6 months, outcome of cognitive dysfunction was mostly stable (supplementary Table S2, available at *Rheumatology* Online).

Discussion

In view of the paucity of high-level evidence, diagnostic and therapeutic decisions in NPSLE are based largely on physician judgement. The EULAR recommendations combined existing evidence and expert consensus, in an effort to facilitate management of NPSLE, especially in places that lack adequate expertise. Nevertheless, guidelines carry the inherent problem of being unable to capture all aspects of clinical practice at all times. To this end, we attempted to juxtapose real-life management of SLE

patients with neuropsychiatric manifestations in two experienced centres with the EULAR recommendations, and to identify areas that may require additional attention.

Notably, the period of our study predominantly included events that occurred before the publication of the EULAR recommendations in 2010. In this regard, the overall good concordance rates between usual care and the recommendations (and the absence of a significant difference in this concordance between events occurring prior to and after publication of the recommendations) is a reassuring observation, as the management of NPSLE has traditionally been based on expert opinion. Moreover, the outcome of NPSLE patients was generally favourable, in accordance with previous reports [16].

A number of interesting observations were made through the comparison of the EULAR recommendations with routine clinical practice in NPSLE patients. First, brain MRI was performed in excess as part of the diagnostic work-up; in cases where its use is not recommended by EULAR, it often failed to reveal any abnormalities and was not useful for diagnosis and management. Neuroimaging with MRI is considered a *sine qua non* in the diagnostic work-up of NPSLE. Despite general agreement about its utility, lack of specificity of conventional MRI remains an issue. Indeed, the percentage of normal brain imaging in our cohort was substantial (~28%), albeit smaller than reported in other recent studies (42–58%) [17, 18]. Specific MRI lesions were present only in cases of CVD and in isolated cases of cranial neuropathy. The most frequent non-specific abnormal MRI finding, periventricular and brainstem WMHIs, was present across all types of manifestation, focal or diffuse, central or peripheral. WMHIs are insufficient to guide therapeutic decisions, as they are also present in SLE patients without neuropsychiatric manifestations and healthy middle-aged individuals [19–21]. However, their presence could imply ongoing small vessel disease in SLE, and their incidental detection in lupus patients may dictate aggressive control of traditional cardiovascular risk factors, including hypertension and hypercholesterolaemia. In this regard, an MRI with white matter pathology, although not specific for diagnosis, can be considered useful in some instances. Conventional MRI will thus remain the procedure of choice for NPSLE, especially for the exclusion of alternative diagnoses. However, as NPSLE is not a uniform entity, application of brain MRI should not follow a one size fits all approach.

An important finding of our study was that 62% of CVD cases occurred in the presence of generalized disease activity, and immunosuppressive therapy (including CYC) was given to most of these patients. Optimal management of stroke in the context of active lupus represents a challenge. Acute CVD management should follow the recommendations for the general population, after consultation with a stroke specialist [22]. Secondary prevention includes anti-platelets or anti-coagulation in cases of aPL-associated thrombotic CVD. However, occurrence of non-embolic CVD in a patient with active/flaring SLE could raise the possibility of a concurrent inflammatory component in the atherothrombotic process. SLE *per se* is considered an independent risk factor for accelerated cardiovascular disease [23], and a recent study showed increased endothelial dysfunction in active SLE, which was reversed after immunosuppressive therapy [24]. Thus, in clinical practice, and especially in the absence of aPL positivity or pathognomonic MRI findings, the inflammatory and thrombotic/ischaemic states in NPSLE are not always possible to differentiate, or they may coexist. To this end, immunosuppressive therapies, along with anti-platelets/anti-coagulation, could be considered to reduce the disease inflammatory burden and its pro-atherothrombotic effects. Our short-term data and unpublished experience with longer follow-up of these patients suggest good outcomes with minimal rates of CVD recurrence. Nevertheless, prospective studies are needed to define the natural history of CVD in the context of SLE, in case antithrombotic therapy is or is not combined with immunosuppression.

A major source of discordance between the EULAR recommendations and routine clinical practice concerned the diagnosis and management of cognitive dysfunction in SLE patients. Although this represents one of the most frequent neuropsychiatric manifestations (up to 80% in some cohorts [25]), the majority of cases have only subtle or mild cognitive deficits that tend to follow a benign course, and only a minority (3–5%) will develop severe cognitive impairment [26, 27]. Although EULAR recommends the ACR 1-h formal battery of neuropsychological tests or the computer-based ANAM for the assessment of cognitive function in patients with SLE, both modalities are time-consuming and require special training, which limits their widespread use in routine clinical practice. Recent studies have attempted to validate simpler screening tools as more convenient and suitable for routine care. While the Cognitive Symptom Inventory questionnaire failed to show association with the ANAM [28], application of the MoCA questionnaire in a small study showed good correlation with ANAM scores, with a sensitivity of 83% [29]. We believe it is reasonable that a simple tool such as the MoCA, due to its user-friendly nature and ease of application, may serve for screening of cognition defects in everyday clinical care. Patients with possible cognitive deficits who fail the cut-off limit should nevertheless be referred for detailed neuropsychological evaluation.

Our study has certain limitations. First, because of its retrospective nature, it cannot be viewed as a validation study. Second, due to the lack of a gold standard for NPSLE diagnosis, it is not possible to calculate sensitivity and specificity values for the EULAR risk factors [30]. Third, the high concordance rates with the EULAR recommendations may be biased by the fact that both study centres are tertiary referral centres with experience in the management of patients with NPSLE. Last, some of the ACR case definitions were underrepresented or not represented at all in our cohort.

In summary, herein we report the first comparison between real-life clinical care of NPSLE patients and the

evidence-based/expert consensus EULAR guidelines. Due to its non-specific and complex presentation, the management of NPSLE will continue to rely on multidisciplinary collaboration and experienced physician intuition. Nevertheless, for centres with less experience in SLE, the EULAR recommendations provide a useful, albeit imperfect, framework for the initial management of patients with neuropsychiatric involvement.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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Coexistence of systemic lupus erythematosus and multiple sclerosis: Prevalence, clinical characteristics, and natural history

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ABSTRACT

Objectives: The coexistence of systemic lupus erythematosus (SLE) and multiple sclerosis (MS) in the same individual has rarely been described. Our objective was to report on the prevalence, clinical characteristics, and prognosis of cases fulfilling the criteria for both SLE and MS.
Methods: We utilized existing patient cohorts from the Departments of Rheumatology and Neurology, University of Crete, and screened patients diagnosed with either SLE ($n = 728$) or MS ($n = 819$) for features of both diseases. The clinical, laboratory, and neuroimaging findings were assessed.
Results: We identified nine patients who fulfilled the diagnostic criteria for both SLE and MS, corresponding to a prevalence rate of 1.0–1.2% in each cohort. All patients were women, with an average age at SLE diagnosis of 42.1 years (range: 34–56 years). The diagnosis of SLE preceded the development of MS in five patients, with a time lag ≤ 5 years in four of them. Initial presentation of MS included spinal symptoms in seven patients. All patients had features of mild SLE with predominantly cutaneous, mucosal, and musculoskeletal manifestations. Accordingly, therapeutic decisions were mainly guided by the severity of the neurological syndrome. During the median follow-up of 4 years (range: 1–10 years), three patients remained stable and the remaining experienced gradual deterioration in their neurological status. SLE remained quiescent in all patients while on standard immunomodulatory MS therapy.
Conclusions: Occurrence of both diseases in the same individual is rare, corroborating data that suggest distinct molecular signatures. SLE and MS coexistence was not associated with a severe phenotype for either entity.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease characterized by multifocal areas of demyelination in the white matter (WM) of the brain and the spinal cord. Its diagnosis necessitates objective evidence of central neurological dysfunction indicative of "dissemination in space and time" (more than one affected area and more than one episode), provided that other possible explanations have been excluded [1]. Systemic lupus erythematosus (SLE), the prototype multisystem autoimmune disease, frequently affects the central nervous system (CNS) and encompasses a wide spectrum of neurologic and psychiatric features (neuropsychiatric SLE; NPSLE) [2].

Although segregation of SLE and MS has been described within families with multiple members affected with autoimmune diseases [3], coexistence of the two disorders in the same individual has only rarely been reported [4–9]. Population-based studies in patients with MS have identified patients diagnosed with additional inflammatory and autoimmune diseases including SLE [10–14]. However, these studies carry the limitations of self-reporting and of data extraction from electronic medical records. Although there is a fair possibility of misclassification and misdiagnosis, such studies provide no detailed description of the clinical characteristics and disease outcomes.

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In the present study, we have utilized hospital-based cohorts of patients diagnosed with SLE and MS who are followed up at the University Hospital of Crete, to identify individuals who fulfill criteria for both diseases (SLE/MS). The island of Crete, located at the southernmost part of the Mediterranean basin, is inhabited by a genetically homogeneous population of approximately 0.6 million individuals, which represents an important resource for genetic and epidemiologic studies in inflammatory and autoimmune diseases [15–17]. We describe the clinical presentation, neuroimaging findings, treatment, and outcome of SLE/MS patients managed in a multidisciplinary approach by both the Rheumatology and Neurology departments. We also report on previously published SLE/MS cases identified through systematic review of the literature and we end with an overview of the current knowledge regarding possible intersection of the two diseases.

Methods

Patients and case definitions

The University Hospital of the University of Crete provides secondary and tertiary medical care and serves as a referral center for the island of Crete (Greece). The Rheumatology and Neurology departments have established electronic-based cohorts for patients diagnosed with SLE and MS, respectively. The SLE cohort is an inception cohort consisting of patients who fulfill either the updated 1997 American College of Rheumatology (ACR) [18,19] or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria [20] and who have undergone at least two consecutive evaluations in our center during the period 1999–2012. MS patients are recruited from the MS Epidemiology Program Project of Crete, which has registered all incident MS cases in Crete during the years 1980–2012, as previously described [15,21]. The diagnosis of MS is based on the clinical and MRI criteria of the International Panel on MS (2010 McDonald criteria [22]). Demographic, socioeconomic, and past medical history data are recorded at baseline visit; clinical, laboratory, imaging data, and therapeutic changes are recorded at all visits.

The two cohorts have been established independently, and for the purpose of this study they were scrutinized; patients diagnosed with both diseases or patients diagnosed with one disease (SLE or MS) who also had features suggestive of the other were reevaluated by an experienced rheumatologist (A.F.) and neurologist (V.M.) to confirm or establish the diagnosis of SLE and MS, respectively. SLE–MS overlap cases were followed up with combined rheumatologic/neurologic evaluation on a regular basis at 3–6 month intervals, depending on disease activity. During patient follow-up, the Safety of Estrogens in Lupus Erythematosus National Assessment—SLE Disease Activity Index (SELENA–SLEDAI) was used to define SLE disease activity and the SLICC damage index for SLE-associated damage. Progression of disability due to MS was assessed with the Expanded Disability Status Scale (EDSS).

Systematic review of the literature

We reviewed the English language literature using the PubMed database from January 1980 to January 2013 with the following index terms: “multiple sclerosis” OR “myelitis” OR “myelopathy” OR “demyelinat*” AND “SLE” OR “lupus” (terms present in title or abstract). Original articles, case series, and case reports were included in the search. Retrieved articles were further scrutinized based on the abstract and/or full-text content. Relevant articles identified by manual search within the reference list of the originally retrieved publications were also included. We included only cases in which the treating physicians had decisively reached a clinical diagnosis of both SLE and MS. We excluded cases of SLE presenting with an MS-like clinical syndrome (referred to as “lupoid sclerosis”) or with neuromyelitis optica (NMO), previously considered to represent an MS variant with optic neuritis and longitudinal transverse myelitis but recently established as a distinct entity characterized by the presence of antibodies against aquaporin-4 [23]. Cases of NMO were identified by inclusion of “myelitis/myelopathy” in the literature search terms. When reported in patients with SLE, these cases were studied in full text and they were considered as cases of SLE–NMO overlap. Figure 1 illustrates the flow diagram of the systematic literature search performed for the identification of the relevant studies.

Results

Case summary

From our cohorts of 728 patients with SLE and 819 patients with MS, we identified a total of nine patients who fulfilled both the criteria for SLE and MS, corresponding to a prevalence rate of 1.0–1.2%. The detailed demographic and clinical characteristics of the patients are presented in Table 1. All patients were Caucasian women, with a median age of SLE diagnosis at 40 years [interquartile range (IQR) = 8 years], which tends to be higher than the usual age of disease presentation. Likewise, in eight cases with SLE and relapsing–remitting MS (RRMS) type, the median age at MS onset was 36 years (IQR = 12 years), which exceeds almost by 6 years the average age of the whole RRMS patient cohort [21]. In five patients, the diagnosis of SLE preceded the development of MS with a time lag of up to 5 years (median = 4 years). In the remaining four patients, the diagnosis of MS was established before the appearance of lupus features (median lag = 5.5 years); one patient with a long-standing history of RRMS developed SLE more than 20 years after MS diagnosis. Antiphospholipid antibodies (aPLs) were present in low titers in two patients (22%, both confirmed 12 weeks apart), but none of them fulfilled the criteria for antiphospholipid syndrome. Specific antibodies against extractable nuclear antigens (anti-SSA/SSB and anti-Sm) were not detected in any patient.

All patients had mild SLE features with cutaneous, mucosal, and musculoskeletal manifestations, only a single patient had a history of pericarditis and major manifestations (i.e., renal, neuropsychiatric, or hematologic) were not observed. Photosensitivity, a feature present in all nine patients, was defined according to the 1987 ACR criteria case definition, with a physician-documented erythematous rash in sun-exposed areas. Regarding the presentation of MS, initial neurologic manifestations stemming from the spinal cord were observed in seven patients (78%); one patient presented with sensorimotor symptoms and another with optic neuritis.

Brain magnetic resonance imaging (MRI) revealed small (<1 cm), focal, discrete, or coalescent infra- and supratentorial, T2-hyper-intense lesions in all patients (Fig. 2). As shown in Table 2, the anatomic distribution of these lesions fulfilled the MRI criteria for dissemination in space (DIS), according to the International Panel on MS (2010 McDonald criteria [22]). Additional imaging findings specific for MS were also present including (a) periventricular ovoid lesions (Dawson's fingers), with typical periventricular location (Fig. 2B), in all patients; (b) lesions adjacent to the temporal horns in eight out of nine patients; (c) lesions in corpus callosum radiating away from the callososeptal interface (Fig. 2D) in seven out of nine patients; and (d) coexistence of iso- and hypo-intense lesions on T1 sequences at the baseline MRI, indicative of different amounts of demyelination and axonal loss, present in all patients. Spinal MRIs revealed focal lesions at the posterolateral portion of the cervical and/or thoracic spinal cord, indicative of MS (Fig. 2A), in eight out of nine patients. Dissemination in time (DIT) was documented by the simultaneous

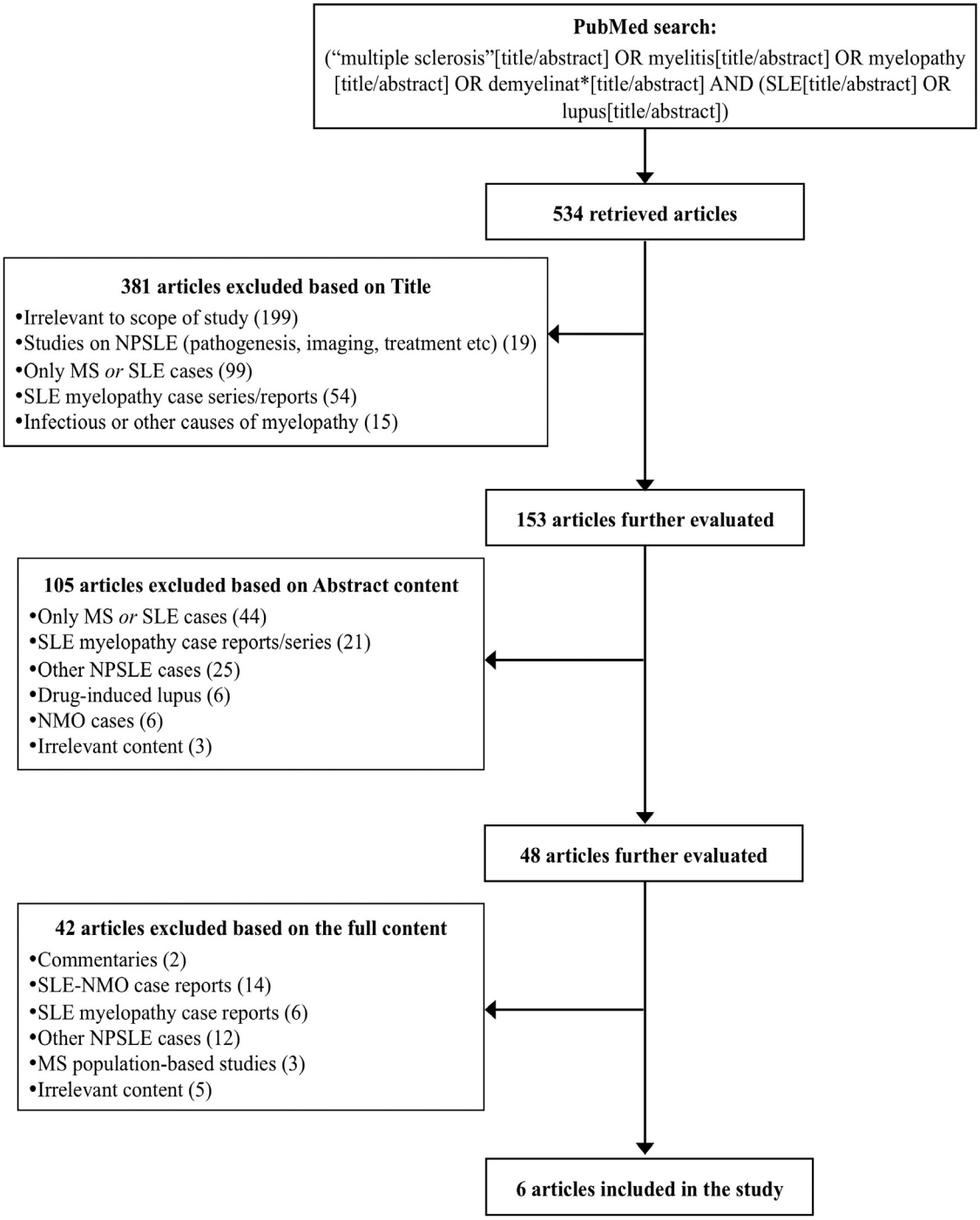

Fig. 1. The systematic literature review. NPSLE = neuropsychiatric SLE; NMO = neuromyelitis optica.

presence of enhancing and non-enhancing lesions at baseline MRI in four out of nine patients and/or new T2-hyper-intense lesions in subsequent MRI scans in all nine patients.

Cerebrospinal fluid (CSF) analysis yielded mild pleocytosis and protein elevation in four patients (44%), whereas intrathecal production of immunoglobulins (either increased IgG index or presence of oligoclonal bands) was observed in six patients (67%). Transcranial magnetic stimulation of the cortex was abnormal (evidence of pyramidal track involvement) in 5/9 patients (56%), visual evoked potentials (VEP) showed evidence of optic neuritis (either subclinical or clinical) in 4/8 patients (50%), and somatosensory evoked potentials (SSEP) were abnormal (i.e., evidence of posterior column dysfunction) in 2/6 (33%) patients.

Five patients (55%) were treated with interferon-β (IFN-β) for control of their neurological symptoms. Two patients (cases 7 and 9, Table 1) were diagnosed with SLE after IFN-β administration (the former, 2.5 years after IFN-β initiation presented with fatigue, prominent arthritis, and ANA positivity, whereas the latter, 1.5 years after IFN-β initiation developed prominent chronic urticaria and hypocomplementemia). However, a targeted history revealed that lupus features (photosensitivity, fatigue, and arthralgias) were evident prior to the initiation of IFN therapy and attribution to the drug was not established after reaching consensus. IFN-β was nevertheless discontinued in the second patient due to the severity of urticaria, necessitating high dose of steroids. In the case of the three patients who received IFN-β treatment

Table 1
Clinical characteristics of SLE–MS patients in our cohort

Patient	Age at diagnosis of SLE/MS	SLE manifestations (set/no. of SLE criteria)	aPLs	Therapy for SLE	SDI	Type of MS	Type of first symptom of MS	Therapy for MS	Progression of EDSS score	MS relapses	Follow-up (years)
1	40/56	Photosensitivity, arthritis, leukopenia, and ANA(+) (ACR/4; SLICC/4)	–	HCQ and AZA	0	RRMS	Spinal	Natalizumab	4.5→5.5	0	1
2	44/21	Photosensitivity, malar rash, arthritis, mouth ulcers, and aPL(+) (ACR/5)	aCL(+)[a]	HCQ and CS	0	RRMS	Spinal	Interferon β	2.5→2.5	6	2
3	36/40	Photosensitivity, arthritis, pericarditis, mouth ulcers, and ANA (+) (ACR/5; SLICC/5)	–	HCQ, AZA, and MTX	0	RRMS	Spinal	Interferon β and rituximab	2.0→2.5	2	7
4	34/39	Photosensitivity, malar rash, arthritis, hair loss, and aPL(+) (SLICC/4)	aβ2GPI(+)[b]	HCQ	0	RRMS	Spinal	Interferon β	2.5→2.5	1	1
5	55/57	Photosensitivity, arthritis, mouth ulcers, and ANA(+) (ACR/4; SLICC/4)	–	HCQ and CS	0	RRMS	Sensorimotor	CS	3.5→4.5	6	6
6	56/60	Photosensitivity, malar rash, arthritis, and ANA(+) (ACR/4)	–	HCQ	0	PPMS	Spinal	CS, AZA, and glatiramer acetate	3.5→6.0	NA	10
7	36/34	Photosensitivity, malar rash, chronic urticaria, arthritis, and ANA(+), ↓C3/C4 (ACR/4; SLICC/4)	–	HCQ and AZA	0	RRMS	Spinal	Interferon β	2.0→2.0	1	4
8	42/36	Photosensitivity, arthritis, leukopenia, and ANA(+) [ACR/4; SLICC/4]	–	HCQ	0	RRMS	Optic neuritis	Glatiramer acetate	2.0→2.0	8	10
9	35/30	Photosensitivity, malar rash, arthritis, ↓C3/C4, and ANA(+) (ACR/4; SLICC/4)	–	HCQ	0	RRMS	Spinal	Interferon β	0.0→3.0	8	5

EDSS = Expanded Disability Status Scale; RRMS = relapsing–remitting MS; PPMS = primary progressive MS; HCQ = hydroxychloroquine CS = corticosteroids; AZA = azathioprine; ANA = antinuclear antibodies; aPL = antiphospholipid antibodies; aβ2GPI = antibodies to β2GPI; aCL = anticardiolipin antibodies; ACR = 1987 revised American College of Rheumatology classification criteria; SLICC = 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria; SDI = SLICC damage index; NA = not applicable.

[a] aCL titer: 30 IgG phospholipid units/ml (normal values <20 IgG phospholipid units/ml).

[b] aβ2GPI titer: 28 U/ml (normal values <20 U/ml).

Fig. 2. A patient (case 3, Table 1) with SLE and MS coexistence. MRI of the spine with T2 sequence in axial plane reveals a hyperintense lesion at the left posterolateral portion of the cervical spinal cord (A, arrow). MRI of the brain with FLAIR sequence in axial (B) and sagittal (D) planes and T2 sequence in axial plane (C), show multiple, hyperintense lesions at the periventricular and subcortical white matter and also at the corona radiata (B), the left posterior part of the upper pons (C, arrow) and the corpus callosum (D). The imaging characteristics and anatomic distribution of the lesions indicate demyelinating disease with dissemination in space, typical of MS.

after SLE had been diagnosed, the decision was based on multidisciplinary (neurologic/rheumatologic) consensus that (a) their lupus was mild and had been quiescent for more than 6 months, (b) the severity of the neurologic (MS) syndrome warranted treatment with an approved agent of established efficacy, and (c) the patients would be under close follow-up (monthly for the first 3 months and then every 3 months) for prompt identification of any signs and symptoms suggestive of SLE flare. None of the patients experienced a lupus flare after several months of follow-up (12, 11, and 6 months, respectively). Other therapeutic modalities for MS included glatiramer acetate (two patients, 25%) and natalizumab and rituximab (one patient each); the latter is reserved for refractory cases with evidence of activity from both diseases, as it is currently off-label for both SLE and MS. SLE treatment consisted of hydroxychloroquine in all patients and occasional short courses of steroids; addition of a second disease-modifying drug (azathioprine or methotrexate) to control disease activity was considered necessary only in three (33%) patients.

The clinical outcome of MS varied; during a median follow-up of 4 years (range: 1–10 years), three patients remained stable, whereas the remaining experienced deterioration in disability. MS relapses were not uncommon with a median (IQR) of 4.0 (5.5) relapses per patient. Nevertheless, disability progression at the end of follow-up, as calculated by the EDSS score, was mild [median (IQR) EDSS increase 0.5 (1.0)] with 6/9 patients showing only residual neurologic symptoms but minimal disability (EDSS ≤ 3.0). In all patients, SLE disease activity remained generally low to moderate (SLEDAI ≤ 6) and no damage accrual was noted.

Literature review

The systematic literature search identified detailed reports of nine cases of SLE/MS coexistence [4–9]. Of note, most studies were published prior to the era of widespread use of MRI, the use of the

Table 2
Anatomic distribution of the MRI lesions identified in the SLE–MS patients of our cohort

Patient	Pons	Cerebellar peduncles	Midbrain	Cerebellum	Periventricular	Corona radiata	Semioval center	Subcortical	Juxtacortical	Corpus callosum	Deep gray matter (thalami and basal ganglia)	Spinal cord
1	–	–	+	–	+	+	+	++	+	–	–	+
2	+	–	+	+	+	+	+	++	++	–	+	+
3	+	+	–	+	+	+++	+++	++	+	+	+	+
4	+	–	–	–	+	+	–	++	++	+	–	+
5	+	+	–	–	+	+	+	+	+	+	–	+
6	+	+	+	–	+	++	+	++	++	+	+	+
7	–	+	+	–	+	+	–	+	+	+	+	–
8	+	–	+	–	+	+	+	+	+	+	–	+
9	+	+	–	–	+	+	+	+	–	+	–	+

+ = less than 5 lesions; ++ = 5–10 lesions; +++ = more than 10 lesions.

McDonald diagnostic criteria for MS, and the full characterization of the NMO entity. Consequently, this raises the possibility of potential misdiagnosis if current diagnostic work-up and classification criteria were to be used *a posteriori*. To this end, we included only cases for which the physician consensus at the time of evaluation had reached the diagnosis of definite MS. Demographics and clinical characteristics are provided in Table 3. All patients were female, the vast majority of Caucasian ancestry and, similarly to our cohort, none fulfilled the criteria for APS. RRMS was the most common MS type (66%), but manifestations at MS onset were more diverse compared to our cohort. In the nine published cases, MS preceded the development of SLE, contrary to our findings wherein the majority (55%) of patients experienced MS symptoms following the diagnosis of SLE. As such, median age at MS diagnosis was markedly different (39.5 years in our cohort as compared to 29.5 years in the published cases), while SLE diagnosis was established at comparable ages (40 years in our cohort versus 39 years in published cases). Unlike our patients who carried a mild SLE phenotype, cases from the literature tended to have more severe SLE, with three patients having at least one major manifestation including CNS, renal, and severe hematologic disease. The lack of detailed description on laboratory parameters, treatment modalities, duration of follow-up, and outcome in many of these reports precluded any further comparisons (Table 4).

Discussion

In this study, we have used hospital-based SLE and MS cohorts at the University of Crete to describe the prevalence, diagnosis, treatment, and prognosis of cases that have both diseases. The University Hospital of Crete is a referral center for patients with possible NPSLE who are routinely managed in a multidisciplinary approach involving rheumatologists, neurologists, psychiatrists, and an experienced neuroradiologist. We found that coexistence of the two disorders reaches an estimated point prevalence of about 1% among patients with SLE or MS. These patients tend to have mild SLE without major extra-CNS organ involvement, which does not require intensive immunosuppressive treatment. MS tends to follow a relapsing–remitting course (frequent relapses), yet with minimal accumulation of disability, and its clinical severity dictates the choice of immunomodulating agents.

The diagnosis of clinically definite MS was established according to the revised McDonald criteria [22]. Traditionally, diagnosis of MS necessitates dissemination of symptoms in space (DIS) and time (DIT), which could take months or years before being established with certainty. To improve sensitivity and allow for earlier MS diagnosis, especially in the case of a clinically isolated syndrome, the 2010 revision of the McDonald criteria simplified interpretation of MRI, so that DIS and DIT can be established from a

Table 3
Summary of published SLE–MS overlap cases in the literature

Case (references)	Age at diagnosis of SLE/MS	SLE manifestations	aPLs	Therapy for SLE	Type of MS	Type of first symptom of MS	Therapy for MS	MS relapses
Case 1 [9]	58/37	Scarring alopecia, leukopenia, and ANA(+)	NR	Topical CS	RRMS	Polysymptomatic	ACTH and probanthine	NR
Case 2 [4]	44/32	Serositis, arthritis, leukopenia, hematuria, and ANA(+)	NR	CS	RRMS	Sensorimotor	NR	NR
Case 3 [4]	34/30	Photosensitivity, serositis, nephritis, arthritis, ANA(+), and anti-dsDNA(+)	NR	NR	RRMS	Brainstem	NR	NR
Case 4 [4]	57/29	Arthritis, ANA(+), anti-dsDNA(+), and ↓C4	(–)	NR	SPMS	Optic neuritis	NR	NR
Case 5 [8]	53/45	Transverse myelitis, thrombocytopenia, ANA (+), anti-dsDNA(+), and ↓ C3/C4	aCL(+) LA(+)	CS and plasma exchange	RRMS	Optic neuritis	CS and carbamazepine	4
Case 6 [7]	11/10	Photosensitivity, malar rash, interstitial nephritis, ANA(+), and anti-dsDNA(+)	NR	CS	RRMS	Spinal	CS	7
Case 7 [5]	NR	Arthritis, oral ulcers, ANA(+), and anti-dsDNA (+)	(–)	NR	PPMS	Spinal	NR	NA
Case 8 [5]	26/21	Arthritis, thrombocytopenia, ANA(+), and anti-dsDNA(+)	aβ2GPI (+)	CS	PPMS	Spinal	NR	NA
Case 9 [6]	32/14	Malar rash, arthritis, ANA(+), and anti-dsDNA (+)	(–)	CS, HCQ, and ASA	RRMS	Polysymptomatic	No therapy	5

aPLs = antiphospholipid antibodies; CS = corticosteroids, HCG = hydroxychloroquine; ASA = acetylsalicylic acid; aCL = anticardiolipin antibodies; LA = lupus anticoagulant; aβ2GPI = antibodies to β2GPI; RRMS = relapsing–remitting MS; PPMS = primary progressive MS; SPMS = secondary progressive MS; ACTH = adrenocorticotropic hormone; NR = not reported; NA = not applicable.

Table 4
Comparison of clinical features between our cohort and previously published cases of SLE/MS coexistence

	Our cohort	Published cases
Gender (female)	9/9 (100%)	9/9 (100%)
Race (Caucasian)	9/9 (100%)	7/9 (78%)
SLE diagnosis prior to MS	5/9 (55%)	0/9 (0%)
ANA(+)	7/9 (78%)	9/9 (100%)
aPLs(+)	2/9 (22%)	2/5 (40%)[a]
Age at SLE diagnosis [median (IQR)]	40 (8)	39 (24)
Age at MS diagnosis [median (IQR)]	39 (24)	30 (14)
No. ACR criteria for SLE [median (IQR)]	4 (0)	4 (2)
Major SLE manifestation[b]	0/9 (0%)	3/9 (33.3%)
Type of MS (RRMS)	8/9 (88.9%)	5/8 (62%)[a]
Most common initial MS manifestation	Spinal (78%)	Spinal (33%)
Fully ambulatory at last follow-up (EDSS $\leq$4.5)	7/9 (78%)	5/9 (5%)

RRMS = relapsing–remitting MS; aPLs = antiphospholipid antibodies; ANA = antinuclear antibodies; IQR = interquartile range.

[a] Not reported in the rest of the cases.

[b] Includes renal, CNS, or severe hematologic disease.

single brain MRI scan [22]. NPSLE, on the other hand, can sometimes present with a clinical picture resembling MS. In the past, the term "lupoid sclerosis" was coined to describe SLE patients with complex neurologic deficits similar to those seen in MS [24]. However, its vague definition was a source of confusion and hence it has now practically been abandoned. The ACR has instead introduced the term "demyelinating syndrome," with diagnostic criteria resembling those of definite MS, which include symptomatic CNS WM lesions, transverse myelopathy, optic neuropathy, diplopia due to nerve palsies or internuclear ophthalmoplegia, and brainstem disease, each occurring at a different time point [25]. The differential diagnosis between the two disorders and the recommended approach to these patients warrants a multidisciplinary approach and briefly includes a thorough clinical evaluation, brain MRI, CSF examination for presence of oligoclonal bands, and nerve conduction studies with somatosensory and visual evoked potentials. In our case series, NPSLE was excluded based on fulfillment of the McDonald criteria for definite MS and the absence of any other SLE-related neuropsychiatric manifestations in all patients.

Although more than one autoimmune disease may aggregate in a particular individual, coexistence of MS and SLE has only rarely been reported. Population-based nationwide studies from various regions have identified MS patients who are diagnosed with additional inflammatory and autoimmune diseases including SLE [78 cases in a total of nearly 22,000 patients with MS (0.3%)] [10–14]. Interestingly, a recent meta-analysis found a trend for increased risk of SLE in patients with MS (odds ratio 2.80, 95% confidence interval: 0.76–10.25), although this association did not reach statistical significance ($p = 0.12$) and there was a significant heterogeneity between studies [26]. Our finding of a higher frequency of SLE/MS coexistence in our cohorts (over 1%) should be interpreted with caution, since our institution is a tertiary referral center for cases with possible SLE or MS. Indeed, accounting for the total population of Crete (623,065 according to 2011 census), the observed prevalence of SLE/MS coexistence approximates 0.001%, which agrees with the combined probability for having both diseases (108 per 10^5 and 100 per 10^5 for MS and SLE, respectively) [15].

Both SLE and MS are considered to develop as a consequence of environmental factors posed upon individuals with a susceptible genetic background. Novel high-throughput technologies have substantially expanded existing knowledge regarding genetics of complex diseases such as these. Genome-wide association studies (GWAS) have confirmed that, apart from loci within the major histocompatibility complex (MHC) that confer the greater risk, multiple non-MHC genes mainly involved in the regulation of immune responses also account for heritability of both SLE and MS [27,28]. In this regard, it is noteworthy that while a lot of the identified autoimmunity loci seem to be shared among multiple autoimmune diseases [29], recent studies suggest that only a limited genetic overlap exists between lupus and other autoimmune diseases, including MS [30]; this implicates that SLE may have a relatively unique non-MHC genetic susceptibility, certainly distinct from MS. At the gene expression level, high-throughput microarray techniques have provided substantial insight into the underlying mechanisms of the two diseases. An initial microarray study showed that genes involved in apoptosis, cell cycle, inflammation, and regulation of matrix metalloproteinase proteins are upregulated in both SLE and MS, thus implicating common pathways [31]. However, subsequent elegant studies have uncovered discrete transcriptome signatures, which include interferon signaling and granulopoiesis in SLE [32,33], as compared to a robust T-cell activation/proliferation in MS [34]. Table 5 summarizes common and distinct genomics and transcriptomics between SLE and MS, along with the cellular functions in which the identified genes are implicated.

A cardinal difference between SLE and MS is the putative role of type I interferons (IFNs) in disease pathogenesis. As stated above, a type I IFN signature is eminent in SLE and peripheral blood mononuclear cells (PBMCs) in active SLE exhibit upregulation of multiple IFN-inducible genes [32]. *In vivo* disruption of the type I

Table 5
Genetic and transcriptomic similarities and discrepancies between SLE and MS, as revealed by novel, high-throughput techniques

Genetic susceptibility	Gene expression
Shared between SLE and MS	
SH2B3 (negative regulator of T-cell receptor signaling)	TRAF5 and CASP8 (apoptosis)
IL12A (T- and NK-cell activation)	CTBP1 (cell cycle)
RPL19P8 (pseudo-gene)	IL11RA and CD19 (inflammation)
CD40 (activation of DCs, B-cells, and macrophages)	TIMP, TGIF, IL1β, and VEGF (regulation of matrix metalloproteinase pathway)
IRF8 (interferon signaling)	
SLE specific	
Dendritic cell function and IFN signaling	Interferon signaling
IRF5, STAT4, SPP1, and IRAK1	IFI35, IFIT1, IFIT3, IFITM1, and OAS1
T-cell function and signaling	Granulopoiesis
PTPN22, TNFSF4, PDCD1, and IL10	MPO, elastase, F2RPA, defensin3
B-cell function and signaling	Immune response
BANK1, BLK, LYN, and BCL6	CCL3, CCR1, CD163, and IL1R2
Immune-complex processing and innate immunity	Protein folding
ITGAM, C1QA, C2, C4A, and C4B	SLP1
Cell cycle, apoptosis, and cellular metabolism	
CASP10, NMNAT2, PTTG1, and ATG5	
Transcriptional regulation	
JAZF1, UHRF1BP1, BCL6, and MECP2	
MS specific	
B-cell function and signaling	T-cell activation and expansion
IL7, IL7R, CD86, CXCR5, and VCAM1	LEF1, TCF3, and SLAM
T-cell function and signaling	
CBLB, EOMES, IL12B, IL2RA, IL7, IL7R, and THEMIS	

IFN pathway has been shown to protect lupus-prone mice from disease development [35]. On the contrary, IFN-β (a type I IFN) constitutes a fundamental treatment option in MS, although the precise mechanism of action remains elusive [36]. While IFN-β administration has been associated with the development of lupus [37], here we observed no flares in patients who received IFN after SLE had been diagnosed. Interestingly, a similarly increased risk for relapses has been observed after IFN administration for treatment of NMO [38]. This observation has led to the hypothesis that SLE may share more features with NMO than with MS; indeed, a significant proportion (44%) of patients with NMO seem to carry ANA [39], while several reports have described occurrence of NMO-spectrum disorders in SLE patients [40]. To this end, serum type I IFN activity and IFN-β-induced responses in PBMCs *in vitro* were found similarly high in SLE and NMO patients, contrasting the low activity in MS patients [41]. Although preliminary, these findings provide initial evidence suggesting distinct pathophysiological pathways between diseases with similar clinical phenotype but markedly different response to the same therapy.

The potential presence of aPL antibodies serves to add more complexity in the clinical scenario of the patient presenting with manifestations suggesting NPSLE or MS. Circulating aPL antibodies are not uncommon in MS, although their prevalence varies widely among studies (2–30%) [42,43]. Conversely, APS may present with a wide variety of neurologic manifestations beyond stroke [44]. In an early study, Cuadrado et al. [45] examined 27 patients initially labeled as "possible MS" with atypical features (atypical imaging findings or evolution, symptoms suggestive of connective tissue disease) who were referred to a lupus clinic; all patients tested positive for aPL and actually fulfilled criteria for APS (either primary or secondary). Notwithstanding the limitation of potential referral bias, this observation led some experts to include APS in the differential diagnosis of MS, especially when the latter presents with atypical findings [46]. In our case series, two of six patients (33%) indeed carried aPLs at low-to-moderate titers, albeit none qualified for a diagnosis of APS and MRI findings were highly suggestive of demyelination.

Conclusion

In summary, we found that approximately 1% of SLE patients in our well-characterized cohort also fulfill the criteria for MS. The coexistence of the two diseases does not seem to be associated with a severe phenotype for either entity although our findings need to be verified in larger, more racially diverse cohorts of patients. The prognosis of these patients, followed by a multidisciplinary group of specialists, is favorable with only slight increase in neurological disability over a 4-year follow-up.

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Pathogenesis and treatment of CNS lupus

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Purpose of review
Neuropsychiatric manifestations pose diagnostic and therapeutic challenges in systemic lupus erythematosus (SLE). We review recently published studies on the epidemiology, pathogenesis, neuroimaging, and treatment of NPSLE.

Recent findings
Generalized SLE activity or damage and antiphospholipid antibodies are identified as major risk factors for neuropsychiatric involvement. NPSLE patients have increased genetic burden and novel genomic approaches are expected to elucidate its pathogenesis. Animal data suggest that, in cases of disturbed blood–brain barrier, autoantibodies against the NR2 subunits of the *N*-methyl-D-aspartate receptor and 16/6 idiotype antibodies may cause diffuse neuropsychiatric manifestations through neuronal apoptosis or brain inflammation; data in humans are still circumstantial. In NPSLE, advanced neuroimaging uncovers structural and metabolic abnormalities in brain regions with normal appearance on conventional MRI. Treatment includes corticosteroids/immunosuppressants for inflammatory manifestations or generalized SLE activity, and antiplatelets/anticoagulation for manifestations related to antiphospholipid antibodies. In refractory cases, uncontrolled studies suggest a beneficial role of rituximab.

Summary
We have begun to better understand how brain-reactive autoantibodies, present in a proportion of SLE patients, can cause brain injury and diffuse NPSLE. Further testing will be required to determine the clinical utility of advanced neuroimaging. Controlled trials are needed to guide therapeutic decisions.

Keywords
autoantibodies, autoimmunity, cyclophosphamide, susceptibility genes, white matter lesions

INTRODUCTION

Neuropsychiatric systemic lupus erythematosus (SLE) involves the central and peripheral nervous system and ranges from overt manifestations such as stroke, seizures, and myelopathy, to more subtle abnormalities such as mood disorders and cognitive impairment [1]. We have previously reviewed the prevalence of NPSLE manifestations and have elaborated evidence-based and expert-based recommendations for their diagnosis and management [2,3]. Herein, we discuss recently published data on epidemiology and risk factors of NPSLE, as well as experimental and neuroimaging studies with implications for the diagnosis and underlying pathophysiology. We end by summarizing the results of therapeutic studies in NPSLE highlighting recent advances in the management of selected neuropsychiatric syndromes in the general adult population.

EPIDEMIOLOGY AND RISK FACTORS

Epidemiological studies have demonstrated increasing prevalence of neuropsychiatric damage in SLE patients during the past 5 decades with a negative impact on survival [4]. Although there is considerable variation in the reported frequency of NPSLE, data from recent large cohorts suggest prevalence rates of approximately 30–40% [5,6]. NPSLE is at least as common in children as it is in adults [7,8] and in a cohort of 232 juvenile SLE in the United Kingdom followed-up over 4.5 years, pediatric BILAG-2004 score for neurologic manifestations showed involvement in 26% [9].

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KEY POINTS

- Advanced neuroimaging can demonstrate subclinical CNS involvement in SLE but its clinical significance is not clear at present.
- Integration of genetic variation with gene expression studies may reveal novel pathogenetic mechanisms in NPSLE.
- Evidence-based and expert-based recommendations are available for the management of NPSLE and may decrease large variations in clinical practice.

The American College of Rheumatology (ACR) research committee has published a set of case definitions for 19 NPSLE syndromes [1]. For each syndrome, diagnostic criteria and a list of alternative, non-SLE-related causes are provided. Fewer than 40–50% of events can be ascribed to underlying lupus central nervous system (CNS) activity ('primary' NPSLE), whereas the remaining are indirectly associated to the disease and can be the consequence of metabolic disturbances, infections, or drug effects ('secondary' NPSLE) [10,11]. Common manifestations such as headache, anxiety, mild forms of depression and cognitive dysfunction are also frequent in the general population and are usually unrelated to SLE. Exclusion of the aforementioned 'minor' syndromes and of polyneuropathy without electrophysiological confirmation reduced NPSLE frequency by almost a half and increased the specificity of ACR nomenclature from 46 to 93% [12]. This was also illustrated in a 3-year prospective study [13] of 370 SLE patients with a mean age of 32 years and no prior CNS manifestations. During follow-up, 76 patients (21%) reported minor CNS complaints and 16 (4.3%) developed one of the following major manifestations: seizures (2.2%), cerebrovascular disease (CVD) (1.6%), myelopathy (1.4%), optic neuritis (0.5%), aseptic meningitis (0.3%), and psychosis (0.3%). These results confirm previous data that the most frequent types of major NPSLE are seizure disorder, CVD, acute confusional state, psychosis, and myelopathy [6,10]. Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, and acute confusional state have been included in the revised Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE [14].

Identification of risk factors for NPSLE is important for providing pathogenetic insights and because their modification could be used for prevention. SLE-related factors repeatedly associated with NPSLE include generalized (nonneurological) SLE activity or damage, history of previous or concurrent other major NPSLE, and antiphospholipid (aPL) antibodies [persistently positive moderate-to-high anticardiolipin (aCL) or antiβ2 GPI IgG/IgM titers or the lupus anticoagulant (LAC)] [2,3]. In the SLICC inception cohort of more than 1000 SLE patients assessed prospectively for up to 10 years, presence of LAC at baseline was associated with subsequent intracranial thrombosis, whereas antiribosomal P was a risk factor for SLE-related psychosis [15]. Higher nonneurological damage and disease activity conferred risk for seizures [16▪]. In a cross-sectional study [17▪▪] of 959 SLE patients, aPL antibodies and/or antiphospholipid syndrome (APS) was the strongest risk factor for primary NPSLE, particularly focal neuropsychiatric events; disease activity and damage also showed association, whereas anti-Ro/SSA antibodies were inversely associated. Other studies have demonstrated relationship between increased SLE disease activity or damage and specific manifestations such as peripheral neuropathy [18] and cognitive dysfunction [19]. Factors not specific to SLE such as increasing age, hypertension, and other atherosclerotic risk factors, have been associated with cognitive dysfunction, depression, and CVD [17▪▪,20–22]. Although these associations are subject to confounding bias and cannot ascertain causal inferences, they suggest a role for disease-driven inflammation and aPL antibody-mediated vasculopathy in NPSLE. Importantly, evaluation for these risk factors, together with information about the timing and type of manifestations and the results from neuroimaging and other laboratory studies, can be helpful in attribution of neuropsychiatric events to SLE (Table 1) [3,17▪▪].

GENETICS OF CNS LUPUS

Large-scale association studies have identified several variants within the Human Leucocyte Antigen (HLA) and non-HLA loci that confer susceptibility to SLE [23]. Although most studies are underpowered to detect distinct genotype–phenotype relationships, there is some evidence for increased genetic burden in NPSLE [24]. In a study [25] of 665 White SLE patients and 1403 controls, the *HLA-DRB1*∗04 genotype and *STAT4* rs10181656 were associated with ischemic CVD, independently of the effects of traditional risk factors and aPL antibody status. Rare mutations in *TREX1*, which encodes for the major 3′–5′ DNA exonuclease, have been reported in sporadic SLE cases, including NPSLE cases [26]. In a large multiancestral study [27], 8372 SLE cases and 7492 controls were screened for a total of 40 common and rare single-nucleotide polymorphisms (SNPs) in *TREX1*. Analysis of SNPs with minor allele

Table 1. Suggested approach to attributing a neuropsychiatric event to systemic lupus erythematosus[a]

Exclusion of secondary causes	Exclusion of infection, hormonal/metabolic disturbances, vitamin deficiencies, drug effects, and association factors reported in the ACR nomenclature and case definitions for NPSLE [1,2,17▪▪]
Type of event: minor versus major	Minor NP events (headache, anxiety, mild forms of depression, and cognitive dysfunction, polyneuropathy without electrophysiological confirmation) are less likely to be attributed to SLE (specificity 46 versus 93% for major NP events) [12]
Timing of event	Most (50–60%) SLE-related events occur at disease onset or within the first 1–2 years after diagnosis; events occurring >6 months before the onset of SLE are less likely to be attributed to SLE [2,10,17▪▪]
Assessment for risk factors for SLE-related event	Major risk factors for SLE-related events include generalized (nonneurological) SLE activity or damage, history of previous or concurrent other major NPSLE, aPL antibodies (persistently positive moderate-to-high aCL or antiβ2 GPI Ig titers, LAC) [2,10,15,17▪▪]
Assessment for risk factors for SLE-unrelated event	Risk factors for SLE-unrelated events include increasing age, atherosclerotic risk factors (hypertension, diabetes, dyslipidemia), heart valvular disease, chronic atrial fibrillation, high cumulative dose of glucocorticoids (>10 g) [2,17▪▪]
Results from neuroimaging studies	MRI abnormalities (small punctuate hyperintense T2-weighted focal lesions in subcortical and periventricular WM, diffuse cortical GM lesions, cerebral atrophy, infarcts) especially when multiple in number and bihemispheric, and in the absence of confounding factors (increased age, atherosclerotic risk factors, heart valvular disease, long-standing lupus) have increased specificity (>70–80%) for primary NPSLE [2,3]
Results from other laboratory studies	CSF abnormalities (pleocytosis, increased protein, low glucose) in the absence of CNS infection are found in 30–40% of active primary NPSLE [2,3]
	EEG activity (spike-wave or unspecific slowing activity) in the absence of brain structural abnormalities has 50–60% sensitivity and specificity for active primary NPSLE; in seizure disorder, epileptiform activity is predictive for seizure recurrence (PPV 73%, NPV 79%) [2,3]
Clinical response to treatment	Clinical response to anti-inflammatory or antiplatelet/anticoagulation treatment favors the attribution to SLE [17▪▪]

ACR, American College of Rheumatology; aCL, anticardiolipin; GM, grey matter; LAC, lupus anticoagulant; NP, neuropsychiatric; SLE, systemic lupus erythematosus; WM, white matter.
[a]The higher number of factors in favor of attribution to SLE, the more likely that the NP event is SLE related.

frequency more than 10% revealed a relatively common risk haplotype in European SLE patients with neurological manifestations, especially seizures. Interestingly, *Trex1*-deficient mice develop lethal autoimmunity associated with increased type I interferon levels, which is relevant to SLE pathogenesis [27,28].

Novel approaches integrating genotyping with gene expression data to identify expression quantitative trait loci (eQTL) are increasingly employed in the study of human diseases. By using a whole-genome array-based assay, Zou *et al.* [29▪▪] quantified 24 526 transcripts in 773 brain samples from the cerebellum and temporal cortex of autopsied patients with Alzheimer's disease and with other brain pathologies. All autopsied patients were genotyped and expression genome-wide association study using 213 528 *cis*-SNPs within ± 100 kb of the tested transcripts was performed. One of the identified eQTL was *IRF5* *cis*-SNP rs4728142 that is associated with both cerebellar *IRF5* expression and risk of SLE [23,29▪▪]. Whether *IRF5* variants are implicated in the pathogenesis of cognitive dysfunction or other neuropsychiatric manifestations in SLE patients remains to be determined.

IMMUNOLOGIC ABERRANCIES IN CNS LUPUS

The pathogenesis of NPSLE involves autoantibody-mediated neuronal or vascular injury, intrathecal production of inflammatory cytokines, disruption of the blood–brain barrier (BBB), and accelerated atherosclerosis [3]. Driven by initial observations in paraneoplastic syndromes, there is increasing appreciation of the role of brain-reactive autoantibodies in the pathogenesis of various neuropsychiatric syndromes [30]. DeGiorgio *et al.* [31] have shown that a subset of anti-DNA antibodies can cross-react with both murine and human NR2 subunits of the *N*-methyl-D-aspartate receptors (NMDAR) and induce neuronal apoptotic cell death. NR2 receptors are abundant in the hippocampus, a brain region implicated in learning and memory processes, and circulating murine and human anti-NR2 antibodies may induce hippocampal apoptosis and cognitive dysfunction in mice in the presence of

breached BBB [32,33]. At low concentration, anti-NR2 antibodies augment NMDAR-mediated excitatory postsynaptic potentials, whereas at high concentration, they cause excitotoxicity through enhanced mitochondrial permeability transition [34]. Another group showed that incubation of human umbilical vein endothelial cells with purified anti-NR2/anti-DNA antibodies from SLE sera upregulated the expression of surface adhesion molecules and the production of interleukin 6 (IL-6) and IL-8 [35▪]. If confirmed, these results suggest a mechanism by which peripherally produced anti-NR2 antibodies can lead to inflammation and BBB disruption, therefore, gaining access to the CNS to initiate NPSLE. Anti-NR2 antibodies are present in the serum or cerebrospinal fluid of 30–40% of SLE patients, and an association with NPSLE – especially cognitive dysfunction and mood disorders – has been reported in some but not all studies [15,36]. Further standardization and validation will be required to determine their clinical utility.

More recently, the 16/6 idiotype antibody, a human anti-single-stranded-DNA antibody originated from a patient with cold agglutinin disease, was shown to hamper visual recognition and spatial memory in intracerebra-ventricularly injected C3H female mice [37▪]. Immunohistochemistry analysis revealed an increase in astrocytes and microglial activation in the hippocampus and amygdala in the autoantibody-injected group [37▪]. Although the relevance of these antibodies in human NPSLE is yet unknown, these findings suggest that brain-reactive autoantibodies with different specificities and at different concentrations might contribute to pathogenesis of diverse neuropsychiatric syndromes in SLE [38].

STRUCTURAL AND FUNCTIONAL CNS ABNORMALITIES IN SYSTEMIC LUPUS ERYTHEMATOSUS

Conventional MRI remains the 'gold standard' in NPSLE imaging due to its wide availability and capability to identify CNS lesions. However, MRI carries significant limitations in terms of sensitivity and specificity not least due to the heterogeneity of NPSLE *per se*. A recent inventory of cerebral abnormalities seen on MRI confirmed that the most frequent pattern in SLE is that of small punctuate hyperintense T2-weighted focal lesions in subcortical and periventricular white matter, usually with no contrast enhancement [39]. The precise role of these lesions in NPSLE remains elusive as similar foci can be found in patients without neuropsychiatric manifestations and in the general population after mid-adult life [40]. Concomitant restricted diffusion of such MRI lesions suggests cytotoxic edema due to focal ischemia but whether this represents frank vasculitis or noninflammatory thrombotic vasculopathy has not been elucidated. Notably, in a subset of NPSLE patients (12%), MRI shows diffuse, cortical lesions in the grey matter, similar to the lesions that develop following seizures [39]. This underrecognized finding is pathophysiologically distinct from white matter lesions and could represent immune response against neuronal components; nevertheless, a clear association between any specific MRI finding and autoantibody-mediated CNS damage is lacking.

More than 40% of SLE patients with various neuropsychiatric manifestations show normal MRI scans [39,41]. For these patients, more advanced imaging techniques have been elaborated to detect subtle aberrations in brain structure or cerebral blood flow. Magnetization transfer imaging, diffusion-weighted MRI, magnetic resonance spectroscopy, functional MRI, perfusion-weighted imaging, have all been applied in NPSLE. These modalities have uncovered abnormalities in the otherwise 'normal-appearing' brain regions in SLE patients with or even without neuropsychiatric manifestations, such as regional grey matter atrophy [42], increased cerebral blood flow [43], and abnormal patterns of brain activation during neurocognitive assessment [44].

PET, which measures metabolic activity by 2–18F-fluoro-2-deoxyglucose (FDG) uptake, has also been employed in NPSLE. Hypermetabolism is thought to reflect active inflammation, whereas decreased FDG uptake is a marker of impending tissue loss and atrophy. The most prevalent finding in active NPSLE is grey matter hypometabolism in the frontal, parietal, or occipital lobe [45]. PET can identify fluctuations in regional cerebral metabolism even in the absence of MRI lesions [46,47]. In a cohort of SLE patients without neuropsychiatric manifestations, PET confirmed grey matter hypometabolism and revealed increased FDG uptake in heavily myelinated white matter tracts correlating with generalized disease activity [48]. This could represent ongoing CNS inflammation early in the course of the disease, and the authors proposed that grey matter disorder (apoptosis/atrophy) might represent a late stage sequel of remote white matter inflammation through a mechanism of diaschisis on areas where these nerve fibers project [48]. Together, and notwithstanding advances in neuroimaging, progress in our understanding of the mechanisms underlying NPSLE has been rather modest, and the diagnostic utility of such techniques remains at present investigational.

TREATMENT OF CNS LUPUS

Treatment of NPSLE is plagued by paucity of controlled trials and current therapeutic approaches remain at large empirical. Corticosteroids, immunosuppressants, antiplatelet/anticoagulant treatment and symptomatic drugs are used depending on the presumptive pathogenic mechanism [2,3]. Immunosuppressive treatment (corticosteroids alone or with immunosuppressants such as azathioprine or cyclophosphamide) is generally indicated for manifestations that are felt to reflect an immune/inflammatory state (acute confusional state, aseptic meningitis, myelitis, cranial, and peripheral neuropathies and psychosis), following exclusion of non-SLE-related causes [2,3]. When manifestations indicate a thrombotic state, particularly CVD especially in the presence of aPL antibodies or APS, antiplatelet or anticoagulation treatment is used [2]. However, clinical practice shows that these two states are not always possible to differentiate or they may coexist. Indeed, in our NPSLE cohort, we found that acute stroke was often accompanied by increased nonneurological SLE activity and that a significant proportion (40%) of patients received immunosuppressive treatment, occasionally with cyclophosphamide, along with antiplatelet or anticoagulation [49]. Thus, although frank CNS vasculitis is recognized as a rare cause of CVD in SLE [2], occurrence of cerebrovascular events in the context of active SLE is not uncommon and may warrant anti-inflammatory treatment as a secondary prevention measure. This holds true especially when aPL antibodies are not present.

Aside from use of immunosuppression in few selected cases, the management of SLE CVD should be similar to the one in patients without SLE. Consultation with a stroke specialist is necessary to identify candidate patients for thrombolysis or other specialized management options. For patients who are not candidate for acute thrombolysis, updated international recommendations consider aspirin as the mainstay for secondary prevention, over clopidogrel, or anticoagulants [50]. In patients with persistently positive, moderate-to-high titers of aPL antibodies, optimal treatment remains a matter of debate, with both advocates of high intensity anticoagulation (target INR >3.0) and supporters of lower intensity or sole antiplatelet treatment [51].

In lupus myelopathy, often associated with aPL antibodies [52], a systematic review concluded that anticoagulation provided no additional benefit over standard immunosuppression [53]. On the contrary, intensive immunosuppression is of paramount importance and a recent report suggests that rituximab may prove a valuable option [54]. B-cell depletion has been used in the treatment of NPSLE, including cases refractory to conventional immunosuppression. Although data come from uncontrolled studies, results are encouraging with more than 80% of patients showing at least partial clinical response [55].

Symptomatic treatment in NPSLE includes anticonvulsants for seizures, antidepressants for mood disorder or antipsychotics medications for psychosis. The role of pharmacologic treatment in cognitive dysfunction remains uncertain, and a controlled study [56] of memantine – a serotoninergic receptor and nicotine acetylcholine receptor antagonist used in Alzheimer's disease – found no significant improvement in cognitive performance against placebo in SLE patients.

OUTCOME OF CNS LUPUS

NPSLE has been associated with increased organ damage and lower health-related quality of life [10]. Major events such as CVD, severe cognitive dysfunction, myelopathy, and optic neuritis often result in significant morbidity and poor functional outcomes [2]. Nevertheless, prompt initiation of immunosuppressive and symptomatic treatment can result in improved long-term outcomes, at least for certain manifestations such as psychosis [57,58] and peripheral neuropathy [18].

CONCLUSION

NPSLE represents a diagnostic and therapeutic challenge due to the wide range of presentations, lack of diagnostic tests with adequate sensitivity and specificity, and limited controlled evidence for selection of optimal treatment. Several pathophysiologic mechanisms may operate and recent studies highlight the possible role of brain-reactive autoantibodies in the pathogenesis of diffuse neuropsychiatric manifestations by altering the function or survival of neurons. Novel neuroimaging modalities enable the detection of subtle structural and metabolic aberrations in brain regions of NPSLE patients. Although these advances enhance our understanding of CNS involvement in SLE, additional studies will be required so that this knowledge can be used for the development of patient-based diagnostic and therapeutic strategies.

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Conflicts of interest

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 666–667).

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