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Demyelinating syndrome in SLE encompasses different subtypes: Do we need new classification criteria? Pooled results from systematic literature review and monocentric cohort analysis

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ABSTRACT

Objective: To describe features of demyelinating syndrome (DS) in systemic lupus erythematosus (SLE).
Methods: A systematic review using a combination of Mesh terms in PubMed and a retrospective analysis of 343 adult patients with SLE were carried out to identify patients with DS. Retrieved cases were classified as affected with DS according to 1999 ACR nomenclature and attributed to SLE by applying the 2015 algorithm. DS defined according to the clinical but not temporal 1999 ACR criteria was classified as clinically isolated syndrome (CIS).
Results: Estimated prevalence of DS (including CIS) in the SLE cohort was 1.3% and incidence rate was 1.5 cases per 1000 patient-years. Overall, 100 cases from literature review and 4 from SLE cohort were identified and are presented as a whole: 49 (47.1%) were classified as neuromyelitis optica spectrum disorders (NMOSD), 29 (27.9%) as CIS, 14 (13.5%) as NMO, 7 (6.7%) as DS prominently involving the brainstem and 5 (4.8%) as DS prominently involving the brain. DS was the SLE onset manifestation in 41 (39.4%) patients. Longitudinally extensive transverse myelitis was the most frequent manifestations being present in 73 (70.2%) patients (37 NMOSD, 21 CIS, 14 NMO, 1 DSB). Methylprednisolone (79.8%) and cyclophosphamide (55.8%) pulses, but also plasma-exchange (16.3%) and rituximab (7.6%) in relapsing-refractory cases, were mostly prescribed. Complete recovery rate ranged between 62% in CIS to 7% in NMO.
Conclusion: DS in SLE is rare (1%) and encompasses different subtypes including CIS. Timely diagnosis and early treatment are recommended to minimize complications.

Demyelinating syndrome (DS) arises as the clinical expression of a loss in myelin, with relative preservation of axons, in the central nervous system (CNS). DS can be classified according to pathogenesis into categories (e.g. demyelination due to inflammatory processes, viral demyelination), that even if simplistic may be useful for diagnosis [1]. Multiple sclerosis (MS) is characterized by white matter (WM) involvement in brain and spinal cord representing the prototype of immune-mediated inflammatory demyelinating diseases [2]. Various diagnostic criteria for MS have been developed and several mimicking conditions such as neuromyelitis optica (NMO), NMO spectrum disorders (NMOSD), transverse myelitis (TM) and acute disseminated encephalomyelitis (ADEM), have been nowadays classified in an effort to increase diagnostic accuracy and efficacy of treatment [3]. Also autoimmune systemic diseases such as systemic lupus erythematosus (SLE), Sjogren's syndrome (SS), Sarcoidosis, or Behçet's disease (BD) may mimic MS or other MS-like disorders [4–7].

In 1999 the American College of Rheumatology (ACR) proposed nomenclature and criteria for neuropsychiatric (NP) SLE [8] and defined DS , previously reported as "lupoid sclerosis", as an acute or relapsing encephalomyelitis with evidence of discrete neurologic lesions distributed in place and time (Table 1). By applying this definition, DS in SLE was estimated to be rare (<1%) [9] and little has been described on clinical characteristics and outcomes of this potentially disabling condition. Noteworthy, whether DS in SLE has different patterns of presentation and progression is still unknown. As an example, many Authors [4,6] reported clinically isolated syndrome (CIS) (Table 1), which accounts for the first episode of MS in 85% of cases [10], as the only manifestation of DS in SLE, but the 1999 ACR criteria fail to classify CIS as NPSLE. Therefore, low ACR criteria accuracy for classification of NPSLE [11,12] and limited knowledge of clinical, laboratory and imaging features of DS in SLE might delay the diagnosis and treatment of this condition, thus negatively affecting prognosis.

The aim of this study was to identify the different clinical subtypes of DS in SLE and to report on their prevalence and clinical features, through

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a systematic review and retrospective analysis of a monocentric SLE cohort.

1. Methods

1.1. Systematic review

Two investigators (EC, MP) independently performed a systematic literature review searching for articles, published between the 1st of January 1945 and the 31st of January 2015, reporting on DS in adult (≥16-year old) patients with SLE.

The search strategy through MEDLINE via PubMed was designed using a combination of the following Mesh terms: "Lupus Erythematosus, Systemic", "Lupus Vasculitis, Central Nervous System", "Demyelinating Diseases", "Leukoencephalopathies", "Vasculitis, Central Nervous System", "Cranial Nerve Diseases", "Diplopia", "Brain Stem". All study types were allowed, but only full publications written in English and providing sufficient clinical data to confirm SLE and DS diagnosis were retrieved. To be included in the review, retrieved papers had to include: 1) patients diagnosed with SLE according to 1982, 1997 or 2012 classification criteria depending on the year of disease presentation; 2a) DS according to ACR nomenclature and case definitions for NPSLE syndromes or 2b) CIS defined as the clinical but not temporal criteria provided by the ACR nomenclature and case definitions for NPSLE syndromes. The 2015 algorithm for attribution of NP events was then applied in order to define the attribution of DS to SLE [13]. The algorithm yields a global score ranging from 0 to 10; where greater the global score higher the probability that NP event could be attributed to SLE. The reported cases were classified in three categories according to the numerical score: "not related to SLE" (score 0 to 3), "uncertain" (score 4 to 6) or "related to SLE" (score 7 to 10). Case reports classified as "not related" and "uncertain attribution" to SLE were excluded.

Once investigators independently selected the articles, initially on the basis of titles and abstracts then on full texts, eligibility and attribution assessment were performed independently in a blind standardized manner. Disagreements between reviewers were solved by consensus. When retrieved studies did not report the characteristics required for eligibility or case classification, corresponding Authors were asked to notify lacking features.

1.2. Longitudinal monocentric cohort analysis

The retrospective analysis of a monocentric cohort of SLE patients was performed. Data were retrieved using the database dedicated to SLE patients followed up at the tertiary Rheumatology Unit, University Hospital of Cagliari (Italy) [14], between the 1st of January 1990 and the 31st December 2015.

For the purposes of this study, cases under investigation were defined as adult patients suffering from SLE with DS according to the same inclusion and attribution criteria used for systematic literature review. Moreover, each patient had to have a complete ascertainment including neurologic, serologic and MRI assessment and must have been followed-up for at least 12 months. The diagnosis of DS was reassessed according to clinical judgment and cases were excluded if explained by other diseases (e.g. MS or infection).

This study was performed according to the principles of Good Clinical Practice and the Declaration of Helsinki.

1.3. Case definition

According to clinical, neurologic, serologic and MRI assessment the cases identified by systematic review and retrospective survey were classified in five different syndromes: A) NMO, according to 2006 revised criteria [15]; B) NMOSD [3,16], with or without brain lesions typical of NMO (hypothalamic, corpus callosal, periventricular or brainstem), including: i) idiopathic single or recurrent events of longitudinally extensive TM (LETM) extending for ≥3 vertebral segments; ii) recurrent or simultaneous bilateral optic neuritis (ON); iii) ON with TM not fulfilling the 2006 revised diagnostic criteria for NMO; C) DS prominently involving the brain (DSB); D) DS prominently involving the brainstem (DSBS); E) CIS consistent with DS secondary to SLE but isolated in time, being or not being isolated in space.

1.4. Outcome definition

Clinical outcomes were defined modifying the physician generated Likert scale for NP events (1 = patient demise, 2 = worse, 3 = no change, 4 = improved, 5 = resolved), proposed by Hanly et al. [17], and evaluated comparing the change in NP status between onset of event and time of final follow-up assessment.

2. Results

2.1. Literature search

The literature search identified 1620 articles but only 75 were included in the study, accounting for 100 case reports (Fig. 1) of which 20 were excluded because not attributable to SLE according to the 2015 algorithm.

Table 1
Definition of (panel A) Demyelinating Syndrome according to the 1999 American College of Rheumatology Nomenclature and Case definition for neuropsychiatric involvement in SLE [8] and (panel B) clinically isolated syndrome according to recent definition [3,10].

Panel A. Demyelinating syndrome according to the 1999 ACR criteria

Acute or relapsing encephalomyelitis with evidence of discrete neurologic lesions distributed in place and time.

Diagnostic criteria:

Two or more of the following, each occurring at different times or one of the following occurring on at least two different occasions.

1) White matter areas of damage within the central nervous system causing limb weakness and sensory loss.
2) Transverse myelopathy*.
3) Optic neuropathy*.
4) Diplopia due to isolated nerve palsies or internuclear ophtalmoplegia.
5) Brain stem (BS) disease with vertigo, vomiting, ataxia, dysarthria or dysphagia.
6) Other cranial nerve palsies*.

*These are also listed as separate case definitions as they can occur as isolated entities. Patients who meet criteria for these and for demyelinating syndrome should be classified as having both.

Panel B. Clinically isolated syndrome

First clinical central nervous system demyelinating event lasting >24 h and isolated in time. It may or may not be isolated in space:

a) ***Isolated in space episode***: single neurologic sign or symptom — for example, an attack of optic neuritis —caused by a single white matter lesion.
b) ***Not isolated in space episode***: more than one sign or symptom — for example, an attack of optic neuritis accompanied by numbness or tingling in the legs — caused by white matter lesions in more than one place.