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Refining the Concept of Lupus-associated Nociplasticity: A Proposal to Subdivide Type 2 SLE Based on Therapeutic Response

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ABSTRACR/INTRODUCTION

Fibromyalgia-like symptoms occur commonly in patients with Systemic Lupus Erythematosus. In 2019, it was proposed that symptoms of Lupus should be characterized as Type 1 and Type 2. Type 1 symptoms such as arthritis, serositis and nephritis are responsive to immunomodulatory treatments and Type 2 symptoms such as fatigue, widespread pain, poor sleep and headache do not respond to anti-inflammatory and immunosuppressive medications.[1] We propose that Type 2 symptoms be subclassified into type 2a and Type 2b as some Type 2 symptoms also respond to immunomodulatory and anti-inflammatory therapies.

Keywords: Systemic Lupus Erythematosus; Lupus; Lupus associated nociplasticity

OPINION AND DISCUSSION

We read with great interest a recent article by Pisetsky et al. on *Nociplasticity: A Proposed Concept to Understand the Symptomatology of Systemic Lupus Erythematosus.*[2] The authors introduce the term "Lupus-associated Nociplasticity" (LAN) to describe Type 2 Systemic Lupus Erythematosus (SLE), which is characterized by widespread pain, fatigue, depression, cognitive dysfunction, and non-restorative sleep. In contrast, Type 1 SLE encompasses inflammatory manifestations, such as arthritis, serositis, and nephritis, that typically respond to immunosuppressive therapy.[1] Notably, Type 2 SLE symptoms resemble those of fibromyalgia and generally do not respond to immunomodulators.[3]

We broadly support the proposed framework for understanding central sensitization due to neuroimmune dysfunction in lupus, and we commend the authors for incorporating LAN into clinical criteria and treatment response assessments. This conceptual advancement has the potential to improve the management of patients with this complex disease. However, based on our clinical experience and review of the literature, we offer several observations:

First, some patients present with fibromyalgia-like symptoms—marked by widespread pain, fatigue, and cognitive impairment—prior to the onset of SLE. These individuals may be more accurately classified as having primary fibromyalgia. Whether neuroimmune dysfunction in such cases is related to a pre-lupus state remains an open question.

Second, certain Type 2 SLE symptoms—such as fatigue, headache, arthralgia and myalgia—sometime improve with immunomodulatory therapy. We propose designating these manifestations as **Type 2a SLE**, as they may correlate with Type 1 disease activity. Importantly, this designation can only be applied retrospectively, based on therapeutic response. Separating these features in this manner may allow for more precise characterization and targeted investigation.

Third, symptoms such as widespread pain, non-restorative sleep, and mood disturbances that persist despite immunosuppressive treatment may be better categorized as **Type 2b SLE**, or secondary fibromyalgia. These patients often benefit from medications such as muscle relaxants, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and gabapentinoids. The LAN concept appears most applicable to this subgroup. It is sometimes difficult to differentiate between Type 2a and Type 2b SLE, but a separation between the two will be helpful considering advances in management of SLE.

In conclusion, we believe that subdividing Type 2 SLE into Type 2a and Type 2b based on treatment response could enhance clinical characterization and improve the design of future trials & therapeutic strategies in SLE.

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