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Hot Topic Lecture

01 MIND ANTIBODIES AND CNS INVOLVEMENT IN SLE: DIFFERENTIAL DIAGNOSES

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Central nervous system involvement in systemic lupus erythematosus (SLE) is a highly important aspect of the disease that is not well understood. It involves several components of the immune system possibly related to certain conditions within the specialised brain compartment.

Important differential diagnoses include the growing spectrum of autoimmune encephalitides. Here, autoimmune mechanisms causing dysfunction of the brain are increasingly recognised and brought about a paradigm shift in neurology and psychiatry. Identification of numerous pathogenic autoantibodies against neuronal tissue resulted in unprecedented diagnostic and therapeutic opportunities. Current clinical and experimental data show that diverse neuropsychiatric abnormalities may be the sole symptoms of brain autoimmunity. Affected patients are at risk that such treatable etiologies are overlooked as rheumatic or psychiatric disorders. In some patients the diagnosis can be made by detection of specific auto-antibodies directed against neuronal or glial surface proteins. These epitopes include voltage-gated potassium channels or glutamate receptors, but also novel antigens not yet tested for autoimmunity, such as cell adhesion molecules or enzymes. The identification and recombinant production of disease-defining human monoclonal autoantibodies from these patients now allow detailed analyses of the pathogenic effects, of signaling cascades leading to neuropsychiatric symptoms and potential triggers of autoimmunity. It has become clear that the perpetual discovery of novel antibodies will continue and ultimately result in a better understanding of pathological mechanisms and therapies in patients with impairment of memory, cognition, affect and mood.

Learning objectives

- Understand important neuropsychiatric differential diagnoses of lupus, in particular autoimmune encephalitis and psychosis
- Review the role of anti–neuronal autoantibodies in autoimmune brain diseases
- Discuss why immediate immunotherapy is important for neuropsychiatric CNS symptoms

Roundtable: Treatment Challenges

01 WHEN AND HOW TO ESCALATE THERAPY IN AN IMPENDING FLARE

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Twenty to thirty percent of patients with systemic lupus erythematosus (SLE) patients experience a disease flare each year. Official definitions are available: The most used are based on physician decisions to change treatment; if treatment is added or escalated, that defines flare. Much research has focused on detecting flares before symptoms occur. The most effective and available is a decline in serum complement levels (C3 or C4), which often precedes symptoms; a recent study showed falling complement has a positive predictive value of 0.74 (very good) and a negative predictive value of 0.90 (excellent).[1] Other biomarkers include rising titers of anti-dsDNA, falling platelet counts and for nephritis increase in proteinuria and appearance of red blood cells in the urine. Other blood markers, less available but probably better, include increased proportions of activated monocytes and naïve B cells, increases in levels of serum cytokine/chemokines ICAM-1 and IP-10, and increased numbers of RBC, platelets or B cells binding the complement split product, C4d. Several urinary biomarkers are likely to predict flares of nephritis, including MCP, NGAL and TWEAK, but these are not consistent across studies. As soon as symptoms of flare begin, the patient saying s/he is flaring is the best sign and is usually accompanied by changes in the laboratory values associated with that individual, such as falling platelet, WBC or RBC counts, increase in proteinuria, rising erythrocyte sedimentation rate, etc. Prevention of flare is a major goal of therapy and the effective treatments that induce improvement also reduce flare rates, including hydroxychloroquine, glucocorticoids, cyclophosphamide, mycophenolate, azathioprine, belimumab, rituximab, and calcineurin inhibitors.

The physician must also rule out other causes of the 'flare' that are NOT SLE. In my experience, fever in an SLE patient is more often a sign of infection than of lupus flare (presence of shaking chills and of very high levels of C-reactive protein are more likely in infection); the urinary tract is the most common source of infection, followed by upper respiratory tract infection and pneumonia, septicemia is also common.[2 3] Appropriate cultures should be obtained before escalating immunosuppression. Risk of infection will be lower if the patient has received all appropriate immunisations and is taking preventive medications while immunosuppressed. Similarly, ischemia of heart, brain, gastrointestinal tract can result from clotting with or without vasculitis, and you may consider anticoagulation while evaluating for active SLE. Serositis can result from uremia. When the physician decides SLE is flaring there are several approaches that suppress flare; probably the quickest is to give an intramuscular dose of long-acting glucocorticoid, such as 40–80 mg of triamcinolone acetonide or 20–40 mg of methylprednisolone acetate, which usually suppresses flare and lasts 2–4 weeks. If flare recurs, increase the daily glucocorticoid dose (patients often do this themselves – before consulting the physician). If there is still disease activity and you cannot taper prednisolone/prednisone to less than 10 mg

daily, increase immunosuppression, either by increasing dose of immunosuppressive being given (e.g. azathioprine) or adding a new immunosuppressive.[4] During this time, consider whether the patient is compliant with the regimen you established prior to flare: Compliance (defined as taking the medication as directed 80% of the time) occurs in only 50–70% of SLE patients: Poor compliance is associated with young patients, those with poor social and economic support systems, less educated, and those with strong beliefs in adverse effects of Western medications and/or utility of other healing approaches.[5] I may choose to use intravenous medications in situations such as these. Most SLE patient use complementary supplements: Those that should be discouraged include St John's wort, which interferes with metabolism of many drugs. Vitamin D levels should be normalised. N-acetylcysteine, polyphenols, omega-3 fatty acids, fish oil and thundervine herb may all have benefits but have not reached general acceptance in the medical community. Since the number of SLE flares is strongly correlated with damage to many body systems, with poor quality of life, and with most of the causes of death of SLE patients, physicians and other caregivers are obligated to identify SLE flares early and suppress them.

Learning objectives

- Differentiate between infection and flare in patients with SLE
- Describe key biomarkers associated with SLE flare
- Explain how best to differentiate infection from SLE flare

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02 MANAGEMENT OF REFRACTORY DISCOID LUPUS

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Discoid lupus erythematosus (DLE) is the most common form of chronic cutaneous lupus erythematosus (CCLE) and occurs as localised form (ca. 80%) or disseminated/generalized form (ca. 20%). The localised form presents with lesions on the face and scalp, especially the cheeks, forehead, ears, nose, and upper lip, whereas the generalized form presents with lesions involving the upper part of the trunk and the extensor aspects of the extremities.[1] The lesions of DLE consist of sharply-demarcated, coin-shaped ('discoid') indurated erythematous plaques with adherent follicular hyperkeratosis.[2] During the course of the disease the lesions may expand at the periphery with an active erythematous border and hyperpigmentation, resulting in atrophy, scarring, telangiectasia and hypopigmentation in the center of the lesions. At the scalp, eyebrows and bearded regions of the face, DLE can progress to total, irreversible scarring alopecia. In the perioral region, the lesions can lead to characteristic pitted acneiform ('vermicular') scarring.[3] Mucosal DLE presents with chronic buccal plaques, showing typical roundish lesions with peripheral white hyperkeratotic striae and central atrophy, erosion or ulceration. Exposure to the sun or irritating stimuli ('Koebner phenomenon'), such as trauma, can provoke or exacerbate the disease.[4] DLE lesions occur in approximately 15–25% of patients in the course of SLE, but more than 95% of patients with DLE lesions suffer from cutaneous disease only. First-line treatment options in DLE include topical corticosteroids or calcineurin inhibitors; in patients with disfiguring and widespread disease, systemic agents need to be applied.[5] The first-line systemic treatment is antimalarials, but some patients are therapy-resistant and immunosuppressive agents, such as methotrexate or mycophenolate mofetil, are used as alternative therapeutic option. The monoclonal antibody belimumab, which is approved for SLE as an adjunct therapy for patients with autoantibody-positive disease who despite standard therapy show high disease activity, may be effective, but needs to be evaluated using validated skin scores.

Learning objectives

- Describe the different types of skin manifestations in DLE
- Explain the preventive strategies for DLE including photoprotection
- Discuss the topical and systemic treatment options for DLE

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03 MEMBRANOUS NEPHROPATHY: HOW AGGRESSIVE SHOULD I BE?

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Compared to proliferative lupus nephritis (PLN), membranous lesions are less inflammatory, have a more benign course, require less aggressive therapy, and have better prognosis.[1] The 2012 EULAR/EDTA recommendations for lupus nephritis[2] were recently updated (Fanouriakis A, *et al* 2019 to be submitted).

Goals of therapy Optimisation (preservation or improvement) of renal function with at least 25% reduction in proteinuria at 3 months, 50% at 6 months and a urine protein/creatinine ratio (UPCR) target below 0.5–0.7 mg/g by 12 months (complete renal response).

Initial therapy Glucocorticoids and immunosuppression if UPCR exceeds 1 mg/g despite the optimal use of renin-