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The Pathophysiology of Systemic Lupus Erythematosus and the Nervous System

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1. Introduction

The pathophysiology of Neuropsychiatric SLE (NPSLE) will be described in this chapter. Systemic Lupus Erythematosus (SLE) is a multiorgan and multisystem autoimmune disorder and its pathophysiology may have protean effects on all components of the nervous system. The central (CNS) and peripheral nervous systems (PNS) may be involved in SLE. About 25 % of SLE may begin in childhood and SLE may present both steadily chronic and more episodic neurologic symptoms as well throughout the life span. The presentation of symptoms and clinical signs is a reflection of the location and type of pathophysiology of the disease in which there is chronic inflammation of varied degrees that may wax and wane. The chronic disease process is responsible for making the CNS for example more vulnerable to lowered seizure threshold and episodic seizures despite the ongoing more chronic pathophysiology involving the inflammation of the blood vessels. The disease may exert effects on peripheral nerves and over time accumulated lesions or immune mediated damage may make tissues more susceptible to damage. Chronic inflammation or immune mediated damage or vasculitis of blood vessels or the vascular supply of the nerves may predispose to neuropathy and lead to progressive deterioration in function over time as lesion burden accumulates in the PNS. Similarly, SLE may also damage various end organs that may impact the nervous system once affected. For example, SLE may impact the heart and cardiovascular system or be associated with antiphospholipid antibodies that may contribute to embolic strokes. Other end organs may be affected for example kidney dysfunction or renal failure that may lead to uremic encephalopathy. Having a rash present or palpable purpura and multiorgan involvement may present clinical clues that SLE is the diagnosis along with clinical evidence of multisystem involvement. Other pathophysiology exists as noted below. In these regards, this chapter seeks to characterize the pathophysiology of the major categories of disease and syndromes on the nervous system in SLE. The categorization of the signs and symptoms and overall disease state and pathophysiology and structures involved will relate to how these conditions are ultimately diagnosed and treated.

Neurologists need to be aware of the varied presentations of SLE as neurologic symptoms may be the first signs or symptoms that come to medical attention for evaluation. Unfortunately since SLE results from chronic and indolently progressive pathophysiology, often only subtle neurologic signs develop insidiously over years and therefore often the diagnosis of SLE may be only possible retrospectively in these regards in some cases.

2. The proposed autoimmune mechanism of SLE on the nervous system and resultant effects

While the definitive mechanisms are unknown, the general principle is that antibodies or immune complexes may attack the blood supply to the neural structures. HLA type may regulate the susceptibility to SLE. Studies of twins seem to indicate that many other factors may work in conjunction with HLA typing to produce clinical disease. Although antineuronal antibodies exist, it is unclear how they exert their effects. Over time, it is thought that progressive inflammation may lead to progressive decline and dysfunction. Recent articles or case reports that delineate that antithyroglobulin antibodies, antimicrosomal antibodies, anti cardiolipin antibodies, B2Glycoprotein I antibodies, antinuclear antibodies, the presence of lupus anticoagulant, and other antibodies may be some of the proposed mediators of immune damage of the CNS. Arguably, much research is needed in this area and complete mechanisms are not understood. SLE mediated attack on tissues is a diverse one including varied mechanisms of deposition of immune complexes, cytokines, and numerous modulators of these activities are postulated to be involved. Studies indicate that there may be attack of neural elements or tissues through the autoantibodies and activated leukocytes.

Medications (such as phenytoin) may produce drug induced lupus, which often spares the kidneys and CNS. The antibody profile of this entity and general immunology however may also differ from non-medication induced SLE. Over time, SLE in the CNS may cause demyelination and various demyelinating syndromes or multiple sclerosis like illness that may seemingly relapse and remit. Similarly a vasculitis may progress either fulminantly or indolently. Multiple yet to be described pathophysiologies may account for the varied syndromes noted below. Varied preponderances or ratios of antibody types in local tissues may also explain somehow whether or nor there is more central or more peripherally mediated neural damage. While the above observations are noted, the mechanism of CNS involvement remains unknown since neither the presence of antineuronal and antiastrocyte antibodies correlate with any CNS pathology or level of involvement. The literature and clinical experience notes that neurological complications may be fulminant or fatal. In general, diagnosis is made on a clinical basis although laboratory confirmation of positive antinuclear antibodies, anti-DNA, anti-RNA, and low complements are supportive in many cases along with identifying other systemic or multiorgan involvement.

3. The importance of the physical and neurological examination: A clinical key to pathophysiology

If SLE or NPSLE is suspected, a careful and detailed meticulous history and physical is mandatory. Specific attention to nearly every organ system in the general medical

examination may yield clues about the presence of an underlying autoimmune or infiltrative or inflammatory disorder. From the moment the patient enters the office, one may notice the malar rash or the anterior tibial vasculitic infiltrative leucocytoclastic mediated rash. Specifically with regards to the neurologic system, a systematic approach should be used in gathering history and examination of mental status, cranial nerves, motor function, reflexes, coordination/cerebellar function, as well as sensory function and gait. Auscultation of the carotid and vertebral arteries, the heart, and looking for Lhermitte's sign and stigmata of emboli are mandatory. Because of the infiltrative nature of SLE, CNS manifestations of the disease include cognitive dysfunction, headaches, confusion, fatigue, depression, mood disorders, demyelinating syndromes, seizures, movement disorders, and strokes. Headaches, depression, fatigue, mood disorders, and cognitive disorders are associated with SLE but the mechanisms of the pathophysiology producing these exact symptoms or syndromes is poorly understood. It is postulated that various degrees of lesion burden in various locations on the CNS may be associated with these symptoms.

In the peripheral nervous system, peripheral nerve damage causing peripheral neuropathy, facial pain, tingling, burning, or numbness may occur. Chronic inflammatory diseases may cause dysfunction of individual named nerves, usually by interfering with their blood supply, thereby causing a mononeuritis or if multiple nerves are involved, a more confluent and diffuse or regionalized mononeuritis multiplex may result over time. Of note, SLE itself or associated treatments such as with corticosteroids that can cause papilledema or pseudotumor.

4. Diagnosing CNS lupus and ancillary testing- a window into the pathophysiology of neuropsychiatric SLE

Laboratory testing may give clues about the pathophysiology of NPSLE. Abnormal CSF is identified in about 50 % of cases with increased mononuclear cells along with oligoclonal bands, and antineuronal antibodies. CT scans and angiograms and MRI scans collectively may be unhelpful when there are no focal findings or if there is mild and diffuse disease, although MRI is the most sensitive radiologic tool to detect virtually any inflammatory, demyelinating, or infiltrative pathology relating to NPSLE. Laboratory markers often do not correlate with neurologic disability although high IgG titers of antineuronal antibodies in CSF may correlate with diffuse disease or high lesion burden on the nervous system. Although 70% of patients may have abnormal electroencephalograms, the findings on the EEG are not necessarily diagnostic of NPSLE by these EEG abnormalities themselves. NPSLE may mimic demyelinating disease and most often the patient may need evidence of multisystem or multiorgan involvement to make the diagnosis. The multiorgan or multisystem manifestations according to previously published guidelines include the presence of malar rash, a discoid rash, the presence of photosensitivity, oral ulcers, arthritis, serositis, renal disease or neurologic or hematologic disorders, or immunologic disorders or the presence of antinuclear antibodies. According to these guidelines if four such clinical criteria are present at any time during the course of the disease, a diagnosis of SLE may be made with 98 % specificity and 97 % sensitivity.

5. CNS disease: General principles

NPSLE may involve as many as 75% of SLE cases according to Johnson and Richardson. Impaired mentation, consciousness, seizures, cranial neuropathies and derangements of

CNS functions may either occur transiently, mildly, or late in the disease as lesion burden accumulates. CSF analysis may be basically normal or show only a mild lymphocytic pleocytosis with an increased protein. According to some sources, most of the central nervous system manifestations can be accounted for the pathophysiology of numerous micro infarcts due to the accumulation of lesions in arterioles and capillaries. The literature postulates that deposition of immune complexes in the vascular endothelium mediates vascular injury and since many patients also have concomitant hypertension, this also affects cerebral blood vessels predisposing them to hemorrhage. As mentioned above, cardiac injury can predispose to embolic complications of endocarditis. Visual complaints are common, especially in children and may include retinal artery occlusion, retinal hemorrhage, cotton wool exudates, papilledema and optic neuritis. Complications of SLE may lead to hypertensive encephalopathy, cerebral vein thrombosis, cranial neuropathies, brainstem dysfunction, and rarely myelopathy. SLE may predispose to bacterial or fungal meningitis or opportunistic infection or cause an aseptic meningitis.

6. Pathophysiology of encephalopathy

Encephalopathy is a general term indicating impaired brain function and this may occur with any amount of brain or CNS involvement in NPSLE. Clinically encephalopathies may present with confusion, lethargy or coma. Encephalopathies may also present more chronically as “brain failure” in which a patient may exhibit dementia or cognitive dysfunction. There are both acute and chronic presentations involving psychiatric symptoms. The literature notes that in general, patients with neuropsychiatric manifestations of SLE in the CNS may have abnormalities on functional neuroimaging and MRI suggesting either a disruption of normal blood flow or a dysregulation of normal metabolic function. Encephalopathies may be due to cerebritis. NSAIDs or nonsteroidal anti-inflammatory drugs may also contribute to encephalopathy by producing aseptic meningitis.

Since many patients with SLE are on chronic immunosuppression, the CNS may be infected with opportunistic organisms and result in meningitis, encephalitis, or abscess. Medications used for treatment of these entities may also contribute or cause encephalopathy.

Posterior Reversible Encephalopathy Syndrome (PRES) generally occurs in patients with uncontrolled hypertension who are on immunosuppression therapy. Renal involvement of SLE is common with PRES. This syndrome may present as a fulminant encephalopathy involving bi-occipital patchy swelling on MRI neuroimaging which has been described in the literature. Fortunately with control of the hypertension, clinical and radiologic reversibility may occur. The pathophysiology of this condition in NPSLE is unknown but is thought to be due to abnormal permeability of blood vessels.

Brain biopsy may be needed to clarify the pathophysiology when MRI findings cannot distinguish cerebritis from another process such as neoplasm like changes or those of opportunistic infection. Meningeal biopsy may be needed to diagnose chronic meningitis when other methods fail in cases of idiopathic chronic encephalopathies.

Focal neurological deficits may result from strokes due to either cardioembolic valvular disease or fulminant vasculitic changes of the cerebrovasculature, or thrombosis associated

with the antiphospholipid antibodies. Dyskinesias may occur and the pathophysiology is thought to be due to the effects of the antiphospholipid antibodies.

7. Pathophysiology of demyelinating disease

SLE may cause changes in both CNS and PNS myelin. The changes may relapse and remit, thereby mimicking attacks of Multiple Sclerosis (MS) like illnesses radiologically and clinically. It should be noted that the neuroimmunology of these conditions may differ substantially, and that the pathophysiology of both entities and the differences are not fully understood. The spectrum of radiological involvement can identify minor and non specific white matter changes to more confluent appearing lesions throughout the neuraxis. NPSLE pathophysiology may therefore mimic what are termed the clinically isolated syndromes of MS such as optic neuritis, transverse myelitis, and more wide spread pathology. A Devic-like syndrome in which there is optic neuritis and changes in the spinal cord is possible, and Devic's disease or Neuromyelitis Optica may be differentiated by the occurrence of NMO antibodies or the presence of antibodies to aquaporin 4 which are noted in Devic's disease.

8. The pathophysiology of seizures in NPSLE

Seizures occur in up to about 25% of patients with NPSLE compared with about 1% in the general population. Seizures may present early in the course of NPSLE. While focal seizures are postulated to be caused from microinfarcts that damage the cortex, systemic derangements and metabolic disturbances and certain medications may cause generalized seizures. Seizures are thought to result from cortical injury from cerebral vasculitis, cardioembolism, or any lesion that may develop within the brain. The presence of cortical location and the presence of cortical hemorrhage or blood products generally increase the likelihood of seizures. The literature indicates that high dose steroid therapy given in pulses is associated with the development of status epilepticus by an unknown mechanism. Focal seizures may also become generalized seizures, and virtually any seizure type may be seen in SLE. Generalized or multifocal onset seizures are common in children with SLE and occur about 10 % of cases. While antiepileptic therapy is often prescribed, these medications do not generally treat what is thought to represent the underlying pathophysiology as the seizures may relate to ongoing inflammation that is somehow contributing to cortical irritability. Nonetheless, many patients are often managed in the short term with anti-seizure medications. Some authors suggest that anti-epileptic medication should be continued until a normal or benign EEG pattern is observed. No study on this however has been performed, and guidelines on how long anti-epileptic medication should continue are lacking. It should be noted that a benign or normal EEG may be seen in patients who have seizure disorders. EEG or EEG monitoring may be useful in patients who may be at risk or have ongoing subclinical status epilepticus during a fulminant NPSLE related encephalopathy but it is unknown if persistence of status epilepticus correlates with a certain type or subset of ongoing pathophysiology of NPSLE in that circumstance. Treatment using antiseizure medications may be useful in an acute setting but these medications do not alter the direct pathophysiology of NPSLE. Since multiorgan failure may contribute to encephalopathy, electrolyte disturbances, or hypertension, treatment of these entities are necessary to

gain control of the seizures that are provoked through those pathophysiologies in NPSLE. The author advises caution in diagnosing patients with first time seizures as idiopathic and in general such patients ought to be seen in follow up to ensure no other systemic or multiorgan involvement may be developing. It may be only in retrospective analysis that these patients might be diagnosed with NPSLE. The epidemiology and pathophysiology of these cases is unknown although the author has noted the subsequent onset of SLE or at least the fulfillment of SLE by clinical criteria over time in several such patients. Since NPSLE is a chronic disease, there may also be a need for lifetime prophylaxis with anti-seizure medications but trials and definitive guidelines on this are lacking, and anecdotally patients with epilepsy and NPSLE may be noted to be best controlled in general when the systemic SLE is controlled.

9. Psychiatric symptoms

Psychosis is common with NPSLE and steroids may accentuate clinical psychiatric features, although an associated cognitive disorder may be temporary or progressive. It may be difficult to distinguish corticosteroid induced encephalopathies with psychiatric symptoms from those of SLE. Since psychiatric symptoms may occur with numerous disease states, these symptoms combined with multisystem involvement of SLE are especially characteristic and may lead to diagnosis. The pathophysiology is unknown although depression and anxiety and psychiatric symptoms may be the initial symptoms of NPSLE. Combinations of depression, anxiety, progressive cognitive dysfunction, and encephalopathy are thought to be mediated by the previously noted mechanisms of chronic inflammation.

10. Vasculitis

Vasculitis in NPSLE often becomes a consideration in patient with autoimmune disease and in young patients with ischemic or hemorrhagic strokes. Patients often have an accompanying encephalopathy, fever, headaches, seizures, and cognitive changes. If there are multifocal levels of neurologic dysfunction, malar rash or palpable purpura present, or an abnormal urine sediment, then SLE as a clinical diagnosis may be likely.

Since angiography typically shows irregular beading and caliber changes of large and medium branches of the anterior, middle, and posterior cerebral arteries, it is believed that the major pathophysiology of vasculitis in NPSLE is due to this finding. While angiography may be positive, histology often shows degeneration within the walls of the smallest blood vessels, while more inflammatory mediators and infiltrates of such are noted in the medium and large vessels. Complete understanding of these mechanisms are being studied. There may ultimately be both inflammatory and non inflammatory processes involved. Aggressive treatment with intravenous steroids and immune modulators are required to treat this often fulminantly presenting, fatal or devastating process.

11. Pathophysiology of ischemic stroke in NPSLE

Ischemic stroke may result from cardiogenic embolism that is due to nonbacterial or from Libman-Sachs endocarditis which occurs on the ventricular or atrial surface of the mitral

valve. The presence of antiphospholipid antibodies may also predispose to strokes and venous thrombosis as previously noted. Ischemic stroke in NPSLE occurs in children and is usually caused by small vessel vasculitis. The literature indicates that stroke may occur in up to 10 % of pediatric series of NPSLE and occur by mechanisms noted above. Thrombotic strokes may present in a more evolving or subacute pattern often with premonitory symptoms, and ischemic ones generally present abruptly with deficits maximally present at onset.

Stroke should be clinically distinguished from hemorrhage and other CNS pathologies and hemorrhage may be likely in association with cardiac emboli or with cerebral venous thrombosis which can also present with seizures.

12. Pathophysiology of chorea in NPSLE

Chorea in NPSLE may precede systemic symptoms of SLE by about 1 year as some articles indicate and can resolve prior to the evolution of other symptoms or signs. The mechanism is unknown. In children, distinguishing this from Sydenham's chorea may be quite difficult since NPSLE may also falsely elevate serum antistreptococcal antibody titres which are characteristically seen in Sydenham's disease. Dopamine blockers such as haloperidol or chlorpromazine may be useful as well as aspirin or corticosteroids. The diagnosis may be made by finding the presence of lupus anticoagulant or with recurrent vascular thrombosis or spontaneous abortions in patients not meeting full criteria for diagnosis of SLE. Chorea in pregnancy (Chorea gravidarum) may also be a manifestation of NPSLE. A pattern of relapsing and remitting chorea of different intensities may suggest NPSLE.

13. Pathophysiology of fatigue in NPSLE

This has been described in the literature and it is suggested that many of such patients do not have evidence of muscle disease or myopathy. Therefore the mechanism is postulated to be due to brain or CNS dysfunction however further details about the pathophysiology is unknown. Depression, myopathy, sleep disorder, and systemic disease may need to be excluded. The literature indicates that chronic orthostatic hypotension should be excluded since this condition also may present with fatigue, although it is not known if infiltration of autonomic nerves in NPSLE is the causative pathophysiology which may actually predispose to orthostatic hypotension.

14. Cranial nerve involvement

Cranial nerve involvement is thought to be rare and transient, generally affecting cranial nerve III. Other cranial nerve involvement has been reported and although the mechanism of cranial neuropathy in NPSLE in general is not fully understood, the pathophysiology is thought to be due to vasculitic changes in the blood supply of the cranial nerves similar to that of a mononeuritis multiplex. While involvement of the nuclei or fascicles of the various cranial nerves is possible within the brain or brainstem, case series and pathologic correlates on this are lacking.

15. Pathophysiology of vision and migraine in NPSLE

The literature indicates that visual and migrainous disturbances occur bilaterally and late in the course of SLE. NPSLE is associated with retinal disease, optic neuritis, and migraine headaches. While the presence of an acute headache in NPSLE could ultimately simply be migraine, it is recommended that one should only make this diagnosis as a diagnosis of exclusion since other encephalopathies, opportunistic infections, meningitis or cerebritis, or venous thromboses or stroke may also present with headache and may occur in SLE.

16. Spinal cord involvement/myelopathy

While this is noted to occur, it is thought to occur rarely. Little literature is available. The author notes experience with patients who have had a fulminant course of CNS disease either from vasculitis or encephalopathy who may also have evidence of myelopathy develop. The mechanism on this and its relative rarity is not well understood. The literature indicates that spinal involvement and pathophysiology in NPSLE is often functionally devastating and may occur acutely, subacutely, or chronically. Syndromes involving a transverse myelitis type presentation, infarction, or the identification of a rapidly expanding type lesion have been described.

17. Peripheral nervous system involvement and neuromuscular disease

Peripheral manifestations of NPSLE involve progressive neuropathy, myopathy, and diseases of the neuromuscular junction(NMJ). NPSLE affecting the NMJ may appear clinically similar to myasthenia gravis. Peripheral neuropathy is postulated to be caused by vasculitic injury to the blood supply of the nerves- the vasa nervorum – which as noted previously produces either a mononeuritis multiplex or a regionalized or more confluent, generalized apparent polyneuropathy. SLE may produce peripheral demyelination. Chronic demyelination can result in a chronic sensory or sensorimotor polyneuropathy. SLE acutely may exhibit pathophysiology present resembling acute inflammatory demyelinating polyradiculoneuropathy or (AIDP) and may mimic Guillian-Barre syndrome. Patients may present with burning or numbness sensations, usually starting distally and as disease progresses and as lesion burden accumulates on the peripheral nerves, more proximal involvement may become evident over time.

Myopathy may result from the inflammatory cascade and may mimic dermatomyositis or polymyositis. One also has to keep in mind that patients diagnosed with SLE may be on chronic steroid regimens. The pathophysiology of steroid regimens may contribute to muscle fiber atrophy without inflammatory infiltrates. Various medications may also contribute to pathophysiology of myopathy in NPSLE.

Distinguishing between neuromuscular disease and polyradiculopathy may be difficult, and EMG, CPK and aldolase testing, and muscle biopsies may be required. CPK/Creatine kinase and aldolase may be mildly elevated in SLE myopathy and may not be able to exclude other causes of myopathy for example from medications.

EMG and Nerve conduction studies(NCS) may provide useful clinical data. In an inflammatory myopathy which would be expected in cases of NPSLE, the EMG may be very active with fibrillations and positive sharp waves and simply may be a marker of muscle irritability. There may be increased insertional activity and myopathic motor units and recruitment abnormalities noted along with complex repetitive discharges. Caution is advised in evaluating patients on treatment for SLE with chronic immunosuppression or steroids since a normal needle examination on EMG may be obtained despite the presence of disease and it is not known how much disease burden is required for this testing to be positive. Repetitive stimulation may be useful in evaluating neuromuscular junction failure or pathology which is rare but described in NPSLE. NCS may identify multiple nerves involved from mononeuritis multiplex, sensory or sensorimotor symmetric distal polyneuropathy, or AIDP (Acute Immune-mediated Demyelinating Polyradiculopathy). Abnormal F waves and H response abnormalities may indicate more proximal root dysfunction.

Nerve biopsy may be useful in identifying active vasculitis as pathology early in the clinical course this may be positive. In more indolent confluent polyneuropathies, there may simply be noted nonspecific demyelination. Muscle biopsy may be used to differentiate inflammatory from other causes of myopathy.

Nerve biopsies may identify inflammatory infiltrates, necrotizing vasculitis in epineurial arterioles or perivascular infiltrates. Immunofluorescence may be useful in identifying immune complexes or complement deposition onto vessel walls. Demyelination or nerve fiber count reduction may be noted.

In Summary, the pathophysiology of NPSLE is complex and mechanisms are at best only partly understood. Hopefully in the future, new developments along multiple lines will lead to a better understanding of the disease state which could lead to additional treatments.

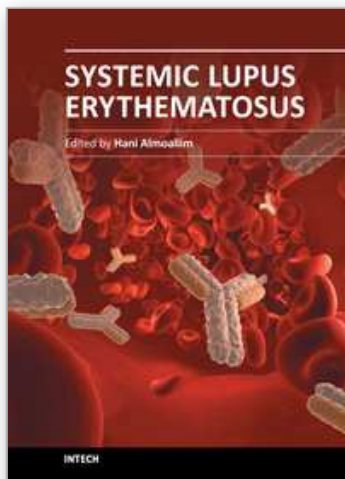
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This book provides a comprehensive overview of the basic and clinical sciences of Systemic Lupus Erythematosus. It is suitable for basic scientists looking for detailed coverage of their areas of interest. It describes how advances in molecular biology have increased our understanding of this disease. It is a valuable clinical resource for practicing clinicians from different disciplines including rheumatologists, rheumatology fellows and residents. This book provides convenient access to information you need about cytokines, genetics, Fas pathway, toll like receptors and atherogenesis in SLE. Animal models have been reviewed as well. How to avoid delay in SLE diagnosis and management, in addition to various clinical manifestations including pregnancy and SLE have all been explained thoroughly in this book.

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