Review Article

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The Wolf'(s)-B(r)ain- The Past, Present, Future of CNS Lupus

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Systemic Lupus Erythematosus is a long-studied condition with protean manifestations, yet, with so much known about the pathogenesis and treatment aspects still in the dark. In this review article, we try to sum up all the knowledge we have till date, the practice essentials used to-date and the future research directions, all of which ultimately lead to a better understanding of the disease and its management.

Key words: Nervous system, Systemic lupus erythematosus

Unlike previously thought, Systemic Lupus Erythematosus (SLE) is a common clinical entity, whose actual numbers are unraveling by the day. This is the prototypic chronic autoimmune condition that has been described since ages. The word "**lupus**" literally means "**wolf's bite**"[1] in Latin. It was coined in the 13th century by *Rogerius*[1], who observed that few of his patients had red colored rashes on their face ("**erythematosus**") which resembled a wolf's bite. As the name suggests this is a "**systemic**" disease which often presents with a plethora of organ involvement. The systemic features were first described by Moriz Kaposi in the 19th century. Even among the organ systems involved, the manifestations can be so diverse that it often warrants a rational clinical suspicion and a thorough evaluation to rule out the disease[2]. Here we review the involvement of the Nervous system affection in SLE in all its aspects.

How common is it?

SLE is a disease of the female gender predominantly (9:1 in US studies[3] and Indian studies show 11:1 towards the female gender[4]). The incidence of SLE ranges from 20-150 per 100,000 population in the US[5]. But Indian epidemiological studies are very scarce with some studies showing incidence of 3.2 per 100,000 population[6]. Given the increasing availability of diagnostic tools and better awareness among patients and doctors these numbers are only headed north.

The neurological involvement of SLE ranges from 14-75%[7]. This is because of the extremely flexible diagnostic criteria proposed by American College of Rheumatology

(ACR) in 1999 when it proposed a set of 19 syndromes of neurological lupus of which 12 had Central Nervous System (CNS) Lupus and seven had Peripheral Nervous System (PNS) Lupus[8,9].

A few Indian studies focusing on the CNS lupus alone, showed that even though the cause for admission in SLE cases to hospital was neurological in only 32% of cases but nearly 78% had one neuropsychiatric manifestation or another[7]. Again, compared to males, females had a higher neurological involvement in SLE. CNS involvement in SLE is usually seen within one year of disease onset and is rarely the heralding organ system to be involved.

Why should we know about CNS Lupus?

CNS involvement usually correlates with high disease activity of SLE. The clinical outcomes of major CNS involvement are pretty grim owing to the delay in presentation (patient factors), delay in recognition and treatment (iatrogenic factors). Compared to the west, the 10-year survival rates of SLE patients in general is a meager 50% in India, compared to an 80% from western data[4]. Hence earlier recognition of the commoner CNS manifestations may lead to an earlier diagnosis and better outcome rates.

Pathogenesis of CNS Lupus

SLE, as described earlier is a chronic auto-immune condition where in the antibodies produced by the body cross react with the host tissues causing the disease. There are a range of antibodies that are known to be associated with SLE, most commonly anti-Smith / RiboNucleoPeptide (RNP), anti-Ro/La, anti-dsDNA among many more[18,19,20,21].

But, as we know the human brain and most of its divisions (except the PNS) are "**IMMUNOLOGICALLY PRIVILEGED**" structures of the body owing to the presence of the omnipresent Blood-Brain-Barrier[10].

Hence it was thought that, for the auto-antibodies which are circulating in the plasma to affect the CNS there can be 2 possible routes. The first if the auto-antibodies are produced in-situ in the CNS; or secondly, if there was a breach in the Blood Brain Barrier, i.e; damage to the microvasculature in the CNS in the form of either a vasculitis or thrombosis (the latter seeming more likely as in APLA). Once the antibodies are in the vicinity of the once cryptic CNS antigens, they bind to the tissues and initiate a cascading complement activation or they may cause deposition of immune complexes; both of which ultimately cause activation of apoptotic pathways and neuronal damage.

This was indeed confirmed by a number of post mortem biopsy studies which showed the presence of a wide variety of pathologies ranging from micro and macro infarcts, bleeds, atrophy, ischemic and patchy demyelination etc. All of them had an underlying common phenomenon of micro-vasculopathy (non-specific) which underlines the fact that disruption of the blood brain barrier is an integral part of the pathogenesis of CNS lupus (highlighted by the fluctuating ICAM-1 levels with disease flares and remissions)[2].

The plethora of manifestations of CNS lupus is due to the fact that in each case the pathology may be different.

There are two scenarios explained regarding the pathogenesis of Neurological Lupus. (Figure 1)

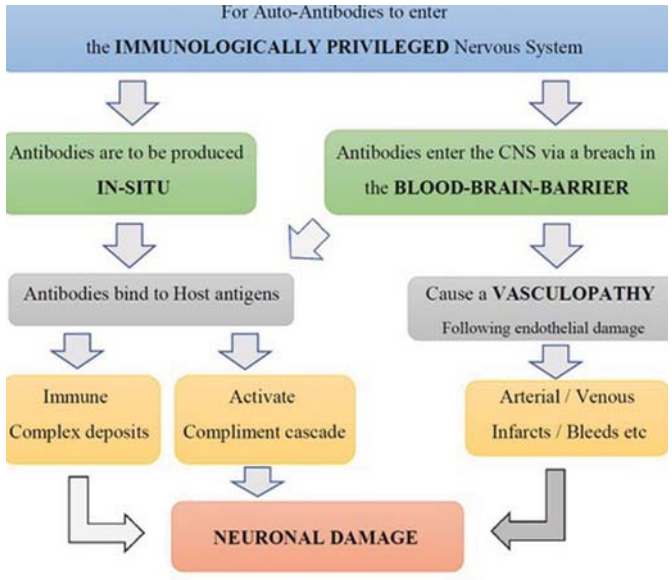

Figure 1 : Pathogenesis of CNS Lupus

Scenario-1 Each antibody type can cross react with a specific receptor in the CNS. DiGiorgio et al showed that the anti-NR2 antibodies cross react with the N-Methyl-D-Aspartate receptors which are richly located in the hippocampus (seat of learning and memory). A number of other intrathecal auto-antibodies are associated with CNS Lupus like the anti-Ribosomal-P antibodies, anti-MAP-2 antibodies. The elevated levels of intrathecal MMP-9 (secreted by the walls of the vasculature mainly) PAI-1, IL-6, IL-8 all are under investigation as markers of disease activity[11,12].

Scenario-2 The patient may present with arterial or venous thrombosis (SLE is a common cause of Stroke in Young). Although most cases are due to commonly associated Anti-Phospho-Lipid antibodies like the Lupus anticoagulant and Anti-Cardiolipin antibodies, which cross react with the phospholipids on the cell wall of the endothelial cells of the microvasculature causing vasculopathy of the vessels leading to either bleeding or thrombosis[13].

CENTRAL NERVOUS SYSTEM			PERIPHERAL NERVOUS SYSTEM	
NEUROLOGICAL SYNDROMES	1.	Aseptic Meningitis	13.	Guillain-Barre syndrome
	2.	Cerebrovascular Disease	14.	Autonomic disorder
	3.	Demyelinating Syndrome	15.	Mononeuropathy (single/multiplex)
	4.	Headache	16.	Myasthenia gravis
	5.	Movement Disorder	17.	Cranial Neuropathy
	6.	Myelopathy	18.	Plexopathy
	7.	Seizure Disorder	19.	Polyneuropathy
	8.	Cognitive dysfunction		
PSYCHIATRIC SYNDROMES	9.	Acute confusional state		
		Anxiety disorder		
	11.	Mood disorder		
		Psychosis		

Table 1: The American College of Rheumatology proposed 19 syndromes of Neuro-Psychiatric SLE[14]

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous 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 physician
5. Non-erosive arthritis	Involving two or more peripheral joints, characterised by tenderness, swelling or effusion
6. Pleuritis or pericarditis	a. Pleuritis—convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion OR b. Pericarditis—documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder	a. Persistent proteinuria > 0.5 g/d or > than 3+ if quantisation not performed OR b. Cellular casts—may be red cell, haemoglobin, granular, tubular or mixed
8. Neurological disorder	a. Seizures—in the absence of offending drugs or known metabolic derangements; e.g. uraemia, ketoacidosis or electrolyte imbalance OR b. Psychosis—in the absence of offending drugs or known metabolic derangements; e.g. uraemia, ketoacidosis or electrolyte imbalance
9. Haematological disorder	a. Haemolytic anaemia—with reticulocytosis OR b. Leucopaenia—<4000/mm^3 on ≥ 2 occasions OR c. Lymphopenia—<1500/mm^3 on ≥ 2 occasions OR d. Thrombocytopaenia—<100,000/mm^3 in the absence of offending drugs
10. Immunological disorder	a. Anti-DNA: antibody to native DNA in abnormal titre OR b. Anti-Sm: presence of antibody to Sm nuclear antigen OR c. Positive finding of antiphospholipid antibodies on 1. An abnormal serum level of IgG or IgM anticardiolipin antibodies 2. A positive test result for lupus anticoagulant using a standard method, or 3. A false-positive test result for at least 6 months confirmed by Treponema pallidum immobilisation or fluorescent treponemal antibody absorption test
11. Positive anti-nuclear antibody	An abnormal titre of anti nuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

Table 2: Showing the American College of Rheumatology criteria of 1997, highlighting the neurological features

Classify a patient as having SLE if **a) The patient satisfies four of the criteria, including at least one clinical criterion and one immunologic criterion or** **b) The patient has biopsy-proven nephritis compatible with SLE and with ANA or anti-dsDNA antibodies**	
CLINICAL CRITERIA	
1. Acute Cutaneous Lupus	Lupus malar rash (do not count if malar discoid), Bullous lupus, Toxic epidermal necrolysis variant of SLE, Maculopapular lupus rash. Photosensitive lupus rash (in the absence of dermatomyositis). Subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, occasionally with post-inflammatory dyspigmentation or telangiectasias)
2.Chronic Cutaneous Lupus	Classical discoid rash-localised (above the neck) or generalised (above and below the neck). Hypertrophic (verrucous)lupus. Lupus panniculitis (profundus). Mucosal lupus. Lupus erythematosus tumidus, Chillblains lupus, Discoid Lupus-lichen planus overlap.
3.Oral ulcers	Palate, Buccal, Tongue or Nasal ulcers (in the absence of other causes, such as vasculitis, Behcets, infection (herpes), IBD, reactive arthritis, and acidic foods)
4.Non-scarring alopecia	Diffuse thinning or hair fragility with visible broken hairs (in the absence of other causes such as alopecia areata, drugs, iron deficiency and androgenic alopecia)
5.Synovitis involving ≥2 joints	Characterized by swelling or effusion or tenderness in 2 or more joints and thirty minutes or more of morning stiffness.
6.Serositis	Typical pleurisy for more than 1 day or pleural effusions or pleural rub. Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day or pericardial effusion Or pericardial rub or pericarditis by ECG (in the absence of other causes, such as infection, uremia, and Dressier's pericarditis)
7.Renal manifestations	Urine protein/creatinine (or 24 hr urine protein) representing 500 mg of protein in 24 hr or red blood cell casts
8.Neurological Manifestations	Seizures, psychosis, Mononeuritis multiplex (in the absence of other known causes such as primary vasculitis), myelitis, peripheral or cranial neuropathy (in the absence of other known causes such as primary vasculitis, infection and diabetes mellitus), acute confusional state (in the absence of other causes, including toxic-metabolic, uremia, drug)
9.Hemolytic anemia	
10.Leucopenia/ Lymphopenia	Leucopenia <4000mm3 at least once (in the absence of other known causes such as Felty's, drugs, and portal hypertension) Lymphopenia <1000mm3 at least once (in the absence of other known causes such as corticosteroids, drugs and infection)
11.Thrombocytopenia	<100,000mm3 at least once (in the absence of other known causes such as drugs, portal hypertension, and TTP)
IMMUNOLOGICAL CRITERIA	
1.ANA	Above the reference range of the laboratory
2.Anti-dsDNA	Above laboratory reference range, except ELISA: twice above laboratory reference range
3.Anti-Sm	
4.Anti Phispholipid Antibody	Lupus anticoagulant, False positive RPR, Medium or high titre anticardiolipin (IgA, IgG or IgM) and beta 2-glycoprotein I (IgA, IgG or IgM)
5.Low Complement	Low C3, C4 or CH50
6.Direct Coombs Test	In the absence of haemolytic anemia

Table 3: Shows the 2012 SLICC criteria to establish a diagnosis of SLE

Role of genetics in neurological lupus:

Although CNS involvement in SLE is common, studies looking at the genetic factors involved in CNS lupus pathogenesis have been rarely conducted. Koga and colleagues in 2011 looked at 282 Japanese SLE patients compared with 222 controls , to assess the cumulative number of risk alleles associated with certain specific genes like HLA-DRB1, IRF5, STAT4, BLK, TNFAIP3, TNIP1, FCGR2B, and TNFSF13 genes [22,23,24,25,26]. There were significantly higher genetic association with the disease than in the control group.

Neurological lupus is a spectrum disorder

Nervous system involvement is one of the most common organ system to bear the brunt of SLE (preceded only by the musculoskeletal and dermatological involvement). The clinical manifestations of Neurological Lupus can be so diverse as it can affect any part of the nervous system. Due to this reason, it is extremely difficult for clinical studies to delineate whether a particular clinical finding is a symptom of the disease or its complication.

Co-evolution of SLE criteria & neurological features with time:

In 1999 The American College of Rheumatology (ACR) came up with a list of 19 diverse clinical syndromes, how neurological lupus may present (Table 1). This was after the initial 1997 ACR criteria for SLE which included CNS manifestations of only seizures and psychosis. (Table 2)

At the time, even though the list was comprehensive it is now being understood that the list is never complete. This is because day by day reports emerge of new associations with SLE like Poly-myositis, Neuro Myelitis Optica, Posterior Reversible Encephalopathy Syndrome

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Table 4: The latest 2019 EULAR-ACR Criteria

etc. This underlines the fact that neurological lupus is indeed a big basket having a diverse spectrum of clinical presentations.

Following this in 2012, an international research group called Systemic Lupus International Collaborating Clinics (SLICC)[16] proposed a revision to the criteria in which they introduced 17 criteria (which had 11 clinical and 6 immunological), elaborated in Table 3. Among the clinical criteria neurological criteria had Seizures, psychosis, Mononeuritis multiplex, Myelitis, Peripheral or Cranial neuropathy and an acute confusional state. This showed that in the period between 1997 to 2012, there was a significant rise in our understanding of the neurological involvement in Lupus.

However, this year in 2019 the European League Against Rheumatism (EULAR) and the American College

of Rheumatology (ACR) came out with a new algorithm for the diagnosis of SLE. In the present EULAR-ACR 2019 criteria[17] the neurological features were trimmed to involve only delirium, psychosis and seizures only. Among them the highest weightage is given to seizures. This has been explained in Table 4.

A number of clinical studies have been carried out with the above criteria. Most studies have found that the most common CNS presentation is headache[15]. (South Indian studies quote an incidence of nearly 55% of all CNS manifestations – with equal incidence of vascular and tension type headaches). But it must be understood that it is the underlying pathogenetic mechanism (either an inflammatory/ vasculopathy) that determines the syndrome which presents to the clinician.

One study in Greece states that among SLE patients with recurrent flares 13% was due to major CNS flares of which the most common manifestations were Seizure disorders followed by strokes, myelopathy, optic neuritis and psychosis (needing admission).

Epileptic attacks coincided with higher disease activity scores, younger age at onset and with antibodies like ANA and ds-DNA. On the other hand, myelopathy was associated with lower disease activity scores, lower compliment and with NMO antibodies along with ANA and ds-DNA. Strokes however were often found to occur secondary to Anti-Phospholipid antibodies.

How do we investigate a case of suspected CNS lupus?

Neurological Lupus is a disease of exclusion. This is because of such diverse presentations of the disease, no single manifestation can be confidently attributed to the disease before excluding all other possible causes. For example: During the workup of a young stroke, if it is found that ANA/ds-DNA is positive; it would be ideal to exclude all other causes using Echocardiography, Homocysteine, Angiograms of the concerned vessels etc before implicating the stroke to SLE.

Immunological testing should be guided by the syndrome of presentation. For example, antibodies like APLA, aCL, anti-beta-GP etc for a thrombotic episode, antibodies like anti-Ribosomal-P for a psychotic episode, antibodies against aquaporin-4 for a myelopathy etc.

Among the radiological investigations, Magnetic Resonance Imaging (MRI) and its advancements such as Spectroscopy, Diffusion weighted imaging, Magnetic Transfer imaging are all useful in identifying the pathology in general but none are considered as gold standard investigation. The same is the case with electrophysiological studies, which can point out a pathology in general but cannot specify or rule out the etiology as SLE.

Due to the lack of specificity of most investigative modalities available as of now, a multi-disciplinary approach is recommended to rule out other causes until the neurological illness can be attributed to SLE.

Management of neurological lupus: Management can be divided into 3 phases[14]:

Symptomatic management

To begin with, the patients must be treated syndromically, i.e.; Anticoagulants and antiplatelets for thrombotic episodes as and when applicable, Antiepileptic medications for seizures etc. One thing of note is to evaluate possible side-effects of drugs used due to the diverse (maybe subclinical involvement of other organ systems in SLE).

Management of an acute flare & long term immuno-modulation

These two entities are discussed together because both are a continuity.

Data from randomized trials for Neurological Lupus management, is available mainly for Cyclophosphamide (in comparison with Methylprednisolone) which found that cyclophosphamide is an ideal immune-modulation to be used in cases of Neurological SLE.

In our experience, for a developing country like India with difficulty in following up patients routinely and also keeping in mind the vast amounts of side-effects associated with oral steroids, we found the use of pulse steroid regimens using Methylprednisolone (in combination with cyclophosphamide) each month for 6 months followed by tapering pulses of steroids provide an equal if not better immune-suppression (for short term flare control). We recommend pulse doses of Methylprednisolone 1gram for 3 days along with Cyclophosphamide dose of 0.75-1g/m^2. This regimen is ideal in cases of SLE causing autoimmune mediated inflammatory diseases, not so much for SLE with thrombotic conditions.

Future – role of biologicals in management of SLE

Targeted biological treatments that modulate aspects of the immune system, have evolved rapidly, as a result of better understanding of the immune pathogenesis. Currently, some novel drugs have appeared in the management of SLE patients, which have shown promising results in phase II, III trials, targeting B cell, T cell, cytokine, and other molecules.

One of the best outcomes was the development of belimumab and rituximab[27,28]. The fully humanized

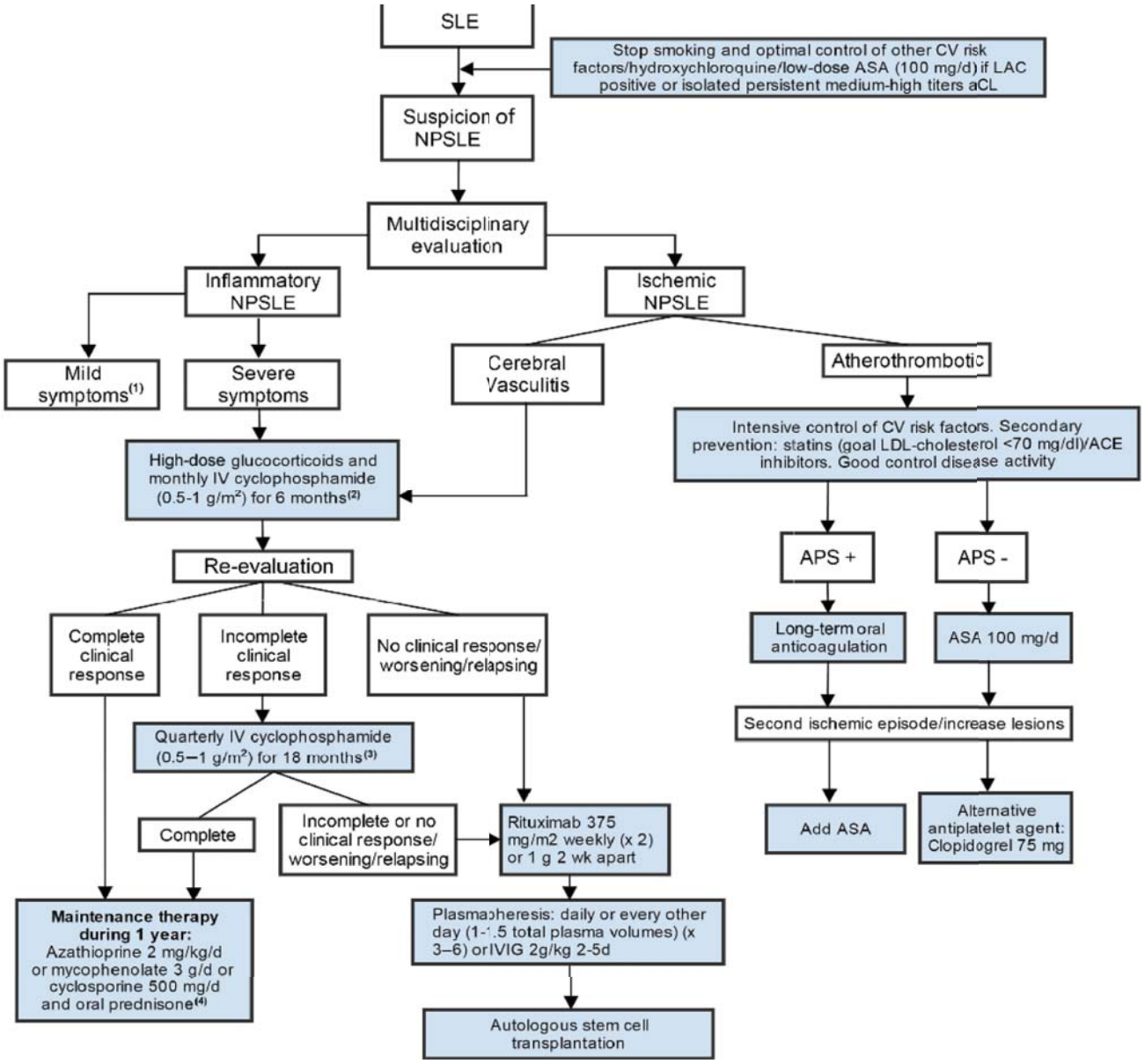

Figure 3. An algorithm for management of Neurological SLE[14]

monoclonal antibody against soluble trimeric B cell activating factor (BAFF), belimumab, has been approved for the treatment of SLE in Europe and the USA[29,30].

Rituximab is another promising option, targeting the CD20 antigen. But lacks data in Neurological Lupus. Most data for rituximab is available with Nephritis from the LUNAR trial. EXPLORER trial evaluated rituximab in non-renal SLE patients and found no significant difference compared to steroids and cyclophosphamide. If more and more data is made available in Neurological Lupus, this drug can be a very good steroid sparing agent with doses to be given every six months. Each cycle is given at a dose of 375 mg/m^2 weekly (repeated after a week).

Stem cells in SLE management

Autologous Hematopoietic Stem Cell Transplantation (HSCT) is one ray of hope for this condition, whose efficacy was established by an international multi-center, open-label phase III, ASTIS trial (Autologous Stem cell Transplantation International Scleroderma)[31,32].

Mesenchymal Stem Cells (MSC) also appears to be a ray of hope for overcoming autoimmunity because of their immunosuppressive properties. MSCs modulate the immune response of different cell populations. Their most important effects are T-cell proliferation and dendritic cell (DC) differentiation inhibition, which are key activating factors of autoimmune disorders. MSCs are effective in

inhibiting proliferation of CD4 and CD8 T cells as well as memory and naïve T cells[33,34].

Data from other immunomodulators like mycophenolate mofetil, azathioprine, methotrexate, cyclosporin are sparse specially for Neurological SLE. A note of caution in our experience is the use of Azathioprine can lead to fatal pancytopenia if the cell counts are not monitored often. Hence use in patients in whom good follow up can be established.

In resistant relapses or flares, Intravenous Immunoglobulins or plasma exchange maybe tried. Immunoglobulins are given at a dose of 2 grams/kg body weight over 3 to 5 days. The exact mechanism how immunoglobulins or plasma exchange helps is still not yet fully ascertained.

Hence in a developing country like India, it would be prudent to prescribe a drug based on individual patient factors and judging the side effect profile to match a suitable drug to a suitable patient.

The following algorithm summarizes the above points as a flow chart in the management of Neurological Lupus[14].

An algorithm for management of Neurological SLE was published in a review by Cesar Magro-Checa et al; in 2016 which summarizes the options as shown[14].

Conclusion

Neurological Lupus is a very commonly encountered problem which often goes unnoticed unless with major CNS involvement. This article directs future researchers to establish more data regarding management of Neurological Lupus. This article emphasizes the importance of recognition and early management of Neurological Lupus to improve the quality of life and reduce the morbidity and mortality rates associated with SLE.

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