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RESEARCH ARTICLE

Chronic Inflammatory Demyelinating Polyneuropathy in Systemic Lupus Erythematosus: A Rare Entity

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Abstract:

Background:

Neurological manifestations in Systemic Lupus Erythematous (SLE) varies and commonly affects the Central Nervous System (CNS) rather than the peripheral nervous system. Neuropsychiatric or CNS manifestation can be as high as 24-54%, whereas the peripheral nervous system involvement is lower around 5-27%. Chronic Inflammatory Demyelinating Polyradiculopathy (CIDP) is one of the three commonest peripheral nervous system involvements in SLE patients and results with severe debilitating effects. However, it is rarely reported.

Methods:

A retrospective review of all SLE patients that were diagnosed with CIDP between 2000 and 2015 was done under follow up at our center that were diagnosed with CIDP between 2000 and 2015. We reviewed their medical records and analyzed their clinical presentation, investigations, treatment instituted, response to therapy and any neurological sequealae.

Results:

A total of 512 case notes were reviewed. Of these 4 patients presented with CIDP (3 females, 1 male) aged between 26 to 46 years old. Three presented with transverse myelitis and the other one with acute motor and sensory axonal neuropathy. All patients were treated with high dose corticosteroids, three patients received cyclophosphamide whilst the other patient was induced with mycophenolate mofetil. Complete recovery was seen in one patient, two had persistent but improving numbness and the other one had a residual weakness.

Conclusion:

Peripheral nervous system involvement in SLE can result in serious debilitating effects. Early diagnosis and treatment are crucial in limiting the neurological sequealae.

Keywords: Chronic inflammatory demyelinating polyradiculopathy, cyclophosphamide, Neurological, Systemic lupus erythematous, Peripheral nervous system, Debilitating effects.

1. INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an autoimmune disease which has diverse clinical manifestation. Neuropsychiatric manifestation of SLE has been reported to be as high as 14 to 80% in adults [1, 2]. The prevalence of peripheral nervous system involvement in SLE is not well established but studies have reported it to vary from 2-13.5%. [3, 4] Common polyneuropathy presentation in SLE includes multiple mononeuritis, acute inflammatory demyelinating

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polyneuropathy and chronic inflammatory demyelinating polyneuropathy [2]. Albeit rare, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is the commonest neurological entity associated with SLE and is being increasingly recognized [5, 6]. CIDP is a chronic, acquired, immune-mediated condition affecting the peripheral nervous system and is characterized by progressive limb weakness, sensory loss and areflexia with a relapsing or progressive course [7, 8]. The first case of CIDP was reported in 1958 in a patient presenting with recurring polyneuropathy that responded to corticosteroid therapy [9]. Subsequently, a diagnostic criteria was proposed by Dyck *et al* in 1975 following a 5-year observation in 53 patients with segmental demyelination [10]. In addition to SLE, CIDP may also be seen in patients with hepatitis C, HIV, malignancies and diabetes [11]. Standard treatment of CIDP is corticosteroids, intravenous immunoglobulin and plasmapheresis [8, 12]. Two-thirds of CIDP patients respond to standard treatment whereas one third can be refractory to the above treatment and may need other immunosuppressive therapies such as cyclophosphamide, mycophenolate mofetil, azathioprine cyclosporin, tacrolimus which can be used to limit corticosteroid and immunoglobulin use [12]. The prognosis in refractory cases is dismal.

Here, we review all our SLE patients that presented with CIDP and report on their clinical manifestations, treatment and progress, and a brief review of the literature on CIDP in SLE patients.

2. METHODOLGY

A retrospective review of all SLE patients (revised ACR criteria) that were under the nephrology clinic at our institution from year 2000 to 2015. We reviewed the case notes of all patients who were diagnosed with CIDP during the course of illness. Their demographic data were studied in particular looking into their clinical presentation, investigation pertaining to the diagnosis of CIDP, treatment instituted, response to therapy and any neurological sequealae. The diagnosis of CIDP was confirmed with either nerve conduction studies that were interpreted by a neurologist or radiological imaging.

We excluded SLE patients with other known causes of neuropathy such as diabetes mellitus, chronic kidney disease and vitamin deficiencies.

3. RESULTS

A total of 512 patients with lupus nephritis were followed up at our institution within this 15 year period. Of these, 4 patients had presented with a diagnosis of peripheral nervous system involvement and their cases are summarized below.

-	Case 1	Case 2	Case 3	Case 4
Age/Gender	46/M	26/ F	35/F	33/F
SLE diagnosis (year)	2008	2007	1998	1999
Onset of CIDP post SLE Diagnosis (months)	8 months	8 months	7 years	13 years
CIDP symptoms	Bilateral quadriceps weakness, normal sensation, normal reflexes	Numbness of right upper limb with loss sensation, light touch and pinprick (C6-T1) and absent reflexes	Bilateral intermittent upper limb numbness with progressive bilateral lower limb weakness.	Neuropathic pain affecting all 4 limbs, with reduced power in both limbs with hyperreflexia
Durations of symptoms	2 weeks	3 weeks	One year	2 weeks
EMG/MRI findings	LP: elevated protein, no oligoclonal bands MRI Brain and Spine: normal NCS: axonal and sensory polyneuropathy	LP: elevated protein MRI Spine: normal NCS: normal	LP: elevated protein, no oligoclonal bands MRI Brain: normal MRI Spine: transverse myelitis hyper intense lesion C3-T2	LP: normal, no oligoclonal bands MRI Spine: hyper intense lesion C5-C7 with cord oedema
Concomitant manifestations	LN Class IV	MSK LN Class IV	Cerebral lupus MSK LN Class III	MSK LN III/V
Antibodies (at diagnosis) C3(NR:86-185 mg/dL) C4(NR:20-59 mg/dL)	C3 69.2 mg/dL C4 21.7mg/dL ANA 1:640 Anti dsDNA negative ACL negative	C3 24.5 mg/dL C4 < 10 mg/dL ANA 1:320 Anti dsDNA positive ACL negative	C3 49.6 mg/dL C4 < 10 mg/dL ANA 1:160 Anti dsDNA negative ACL negative	C3 99.2 mg/dL C4 14.1 mg/dL ANA 1:160 Anti dsDNA positive ACL negative

(Table) contd.....

-	Case 1	Case 2	Case 3	Case 4
Treatment	Corticosteroids, Mycophenolate mofetil, gabapentin	Corticosteroids, Plasmapheresis, IV Immunglobulin IV Cyclophosphamide for one year then maintained with mycophenolate mofetil and ciclosporin A	Corticosteroids, Plasmapheresis, IV Immunoglobulin, IV cyclophosphamide then maintained with mycophenolate mofetil	Corticosteroids, IV cyclophosphamide then maintained with myfortic and tacrolimus
Outcome	Symptoms resolved gradually over one year	Relapsed with new onset of numbness & reduced sensation in T4 -T10 dermatomes whilst on treatment with IV cyclophosphamide for 18 months Six months later symptoms recurred and repeat MRI demonstrated transverse myelitis C1-C7 Persistent numbness despite SLE being in complete remission but ADL independent	Relapsed 8 years later with generalized tonic clonic seizures and bilateral numbness and weakness of both limbs with hyperreflexia. MRI Brain and Spine: hyperintense C3- T3 lesions Treated as relapsed CNS lupus with IV cyclophosphamide Symptoms persist but ADL independent	Symptoms improved gradually over 6 months
Follow up (years)	8 years	7 years	18 years	17 years

4. DISCUSSION

CIDP in SLE patients has been increasingly gathering the attention of clinicians despite its unclear pathophysiology. It is believed to be an autoimmune condition whereby there is the production of antibodies against gangliosides (especially towards GM1 and GM3) [8]. These antibodies destroy the myelin sheath and axon resulting in polyneuropathy [13]. The prevalence of CIDP is between 2-5 cases/100,000 individuals in the general population but there is no data in SLE patients [14]. Neuropsychiatric syndromes of SLE in adults develop before or around the diagnosis SLE in 30-70% of patients [15, 16]. Two of our patients developed CIDP around the time of SLE diagnosis whereas in the other two, it developed many years later during the course of their disease.

The clinical presentation of CIDP varies depending on the nerve involvement as illustrated in our case series. Typically they either present with chronic progressive, stepwise progressive or relapsing weakness with symmetrical involvement of proximal and distal muscles and sparing of extraocular muscles [10, 17]. Even though our case series is in a younger age group, they had a chronic progressive course like the reported literature in the majority of elderly patients with CIDP [18]. CIDP can mimic Guillian Barre syndrome but they rarely develop respiratory failure and is not preceded by an infection [19, 20].

Pure motor presentation affects up to 10% of cases whilst the sensory variant affects 35% of the cases whereas the remaining 50% present with a combination of sensory and motors symptoms [21, 22]. Three out of our four patients presented with sensory symptoms and three had weakness. In case 1, he exhibited typical bilateral symmetrical motor neuropathy with normal sensory while case 4 developed limbs weakness with hypereflexia. Case 2 had areflexia with sensory involvement however power was relatively normal. In all the cases reported, case 3 was the one that exhibited most manifestations of neuropsychiatric SLE ranging from cerebral lupus, mood disorders, seizures, aseptic meningitis to CIDP.

The most important laboratory studies that support the diagnosis of CIDP are Cerebrospinal Fluid (CSF) examination, Nerve Conduction Studies (NCS) and Magnetic Resonance Imaging (MRI). Of these CSF evaluation is the most sensitive as protein is elevated in up to 94% of cases and in keeping with our findings [23]. Oligoclonal bands are identified in the CSF in up to 65% of CIDP patients but we did not demonstrate this in our patients [11]. Nerve conduction studies or electromyography is the investigation of choice to confirm the diagnosis of CIDP. However, it bears no significance or impact in terms of severity or prognosis of CIDP. Only two of our patients had NCS as the other two patients had MRI findings in keeping with CIDP. Typical MRI findings include thickened or swollen gadolinium enhancing roots or plexuses on a T2 weighted image [11]. Such findings were present in three of our patients either during initial presentation or relapse.

Studies have demonstrated positive anticardiolipin antibody of IgG and IgM has a strong correlation with neurological lesions detected by the electromyography than those without antibodies [24]. However, in our case series, we could not demonstrate this finding.

Treatment goals are to improve muscle strength and patients' quality of life [8]. Corticosteroids are used as first-line due to its anti-inflammatory properties and all our patients received high dose corticosteroids. An alternative to corticosteroids is Intravenous Immunoglobulin (IVIG) for 3 to 5 days with or without Plasma exchange [7, 8, 12].IVIG responder could see the effect within 1-3 months and it is best used if the symptoms occurred less than one year with extremities involvement, however, the response was reported to be poor in those with multiorgan involvement with multiple SLE autoantibodies [16]. In our case series, two patients received IVIG with plasmapharesis in addition to steroid treatment.

Studies have shown that about one-third of CIDP patients will be partially responsive or refractory to standard mentioned therapy requiring second-line immunosuppressive therapy such as azathioprine, cyclosporin A, mycophenolate Mofetil or cyclophosphamide [8]. Intravenous pulsed Cyclophosphamide in both intravenous pulsed or oral has been shown to be effective in patients' refractory to IVIG, plasma exchange or corticosteroids with an average time for improvement to be 8.5 months [25, 26]. We chose cyclophosphamide in three of our patients as a second line agent as they also had concomitant lupus nephritis for which it is the mainstay of induction therapy. These patients were then maintained on with mycophenolate mofetil ± calcineurin inhibitor together with low dose corticosteroid.

Anecdotal reports have shown promising effects with monoclonal antibodies such as Rituximab, Alemtuzumab and Eculizumab [8]. Rituximab is more widely reported compared to the other biologics and been used either as first line or as an adjunct treatment in refractory cases. Rituximab is an anti CD 20 antibody on B-lymphocytes which causes depletion of B cells resulting in a reduction of antigen-antibody complex. Few studies have reported a satisfactory response with rituximab in patients with refractory CIDP [27 - 29]. In our cases, none of them received rituximab despite case 3 being counseled for it.

Studies have shown that 90% of CIDP patients respond to immunosuppressive therapy however they have a high relapse rate of up to 50% [23]. The 2007 CIDP outcomes survey demonstrated that despite advances in the treatment and care of CIDP patients, neurological prognosis remains poor with majority end up with some degree of disability and one-third of them require an assistive device to ambulate [30]. In our case series, two of our four patients had persistent symptoms but were able to ambulate unaided.

CONCLUSION

There are still limited numbers of randomized clinical trials on CIDP in SLE in view of its scarcity. Our case series describes the clinical presentation, diagnostic tools used, the therapeutic armamentarium and outcomes in CIDP. We believe cyclophosphamide is safe and efficacious in treating CIDP. Early diagnosis and treatment are crucial in limiting the neurological sequealae.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for the studies that are bases of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest, financial or otherwise.

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Declared none.

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