AFRICAN JOURNAL OF MEDICINE and medical sciences

Volume 38 Number 1 March 2009

ISSN 1116—4077

Afr. J. Med. Med. Sci. (2009) 38, 33-38

Neuropsychiatric systemic lupus erythematosus among Nigerians

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Summary
Systemic Lupus Erythematosus (SLE) and concomitant complication of Neuropsychiatric lupus (NPSLE) are rarely reported among Africans. This retrospective study has the objectives of highlighting the clinical and laboratory characteristics of SLE subjects with neuropsychiatric manifestations seen in a private practice rheumatology clinic and comparing these with studies elsewhere. Such subjects were diagnosed using the American College of Rheumatology (ACR) criteria for SLE as well as the ACR Case definition for Neuropsychiatric SLE (NPSLE). A total of thirty three subjects (51.6%) out of the sixty four diagnosed SLE had features of NPSLE. Females were more commonly affected and the mean age was 32.8 years. Most of the subjects had either one or two concomitant syndromes. Headache was the commonest presentation (66.6%) while other common presentations were seizures (42.4),psychosis (30.3%) were also seen. Dementia was the least seen. The mean erythrocyte sedimentation rate was 95.5mm/hr. Serology tests showed high frequencies of Anti Nuclear Antibody (ANA) and Anti ds DNA. Treatment was with standard immunosuppressives, and epileptics where indicated. The outcome was generally good with 54.5% better after six months while 7 subjects (21%) were lost to follow up and three were known to have died. NPSLE is a common presentation among Nigerian SLE patients and the pattern is as seen in other reports, though the frequencies of the syndromes vary widely. Early recognition and management with immunosuppressives are required.

Keywords: *Lupus neuropsychiatric syndromes Nigerians*

Résumé
Cette étude rétrospective a pour objectif d'illuminer les caractéristiques cliniques et laboratoires des sujets ayant SLE avec les manifestations neuropsychiatriques observé dans la clinique privée de rhumatologie et comparé avec d'autres études effectuées ailleurs. De tels sujets étaient diagnostiqués utilisant Les critéres du Collége Americain de Rhumatologie (CAR) pour le SLE aussi bien que des cas défini de neuropsychiatrie SLE (NPSLE). Au total 33 sujets (51.6%) sur soixante quatre cas diagnostiqués avaient les caractéristiques du NPSLE. Les fêmeles étaient plus affectées et la moyenne d'age était de 32.8 ans. La plupart des sujets avaient soit une ou deux syndromes concomitant. Les maux de tête était le symptome clinique le plus commun (66.6%) alorsque d'autres présentations cliniques ,les convulsions (42.4) et les psychoses (30.3%) étaient observées. Dementie était le moindre symptome observée. Le taux moyen de sédimentation était de 95.5mm/hr. Les tests sérologiques montraient les fréquences élevées d'anticorps anti nucléaires (AAN) et Anti ADN. Le traitement était á l'aide des immunosuppressants standard, et les épileptiques ou indiqués. Generalement, le résultat était satisfaisant avec 54.5% mieux après 6 mois, bien que 7 sujets (21%) perdaient de suivi et trois décés. Le NPSLE est une présentation commune parmi les SLE patients Nigérian et la fréquence semblable á d'autres rapports, bienque les fréquences des syndromes variant grandement. La détection précose et les soins á l'aide des immunosuppressants sont nécessaire.

Introduction

Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) constitutes a wide array of neurologic syndromes associated with SLE. These syndromes include central, peripheral, autonomic nervous system and psychiatric features, mostly associated with the disease, but sometimes attributed to the medications used. NPSLE can occur at any stage of the disease, sometimes even before the obvious skin and musculoskeletal manifestations. [1, 2].

Varieties of the syndromes described include cerebrovascular disease, headache, demyelinating syndromes, movement disorders, myelopathy, seizure disorders, psychosis, cognitive dysfunction, neuropathies and autonomic disorders among others [3, 4, 5, 6, 7].

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A Committee of American College of Rheumatology (ACR) has proposed case definitions for 19 neuropsychiatric syndromes seen in SLE, with reporting standards and recommendations for laboratory and imaging tests [7]. The committee also suggested serological tests such as the Antiphospholipid antibodies (APA) and Anti-ribosomal P as strongly correlating tests in NPSLE. Structural investigations include CT scan, MRI, ECG and EMG. While these imaging investigations are by no means diagnostic, they may be useful in excluding conditions that have the same clinical presentations in practice.

The occurrence of NPSLE is usually associated with more frequent use of corticosteroids and immunosuppressive drugs. It is also associated with a significant reduction in quality of life [8]. Predictive factors for NPSLE include SLE disease activity and severity, Caucasian race, presence of APA or Anti Ro/SSA. Baseline features such as higher disease activity are predictive of psychosis and cognitive impairment while presence of Anti ds DNA are predictive of polyneuropathy. The presence of anti phospholipid antibodies has been found to be predictive of seizures and CVA [9].

The risks of seizure and epilepsy have also been reported to be associated with a higher disease activity at baseline, prior neuropsychiatric SLE as well as Anti cardiolipin and Anti-Sm antibodies [10] Psychiatric abnormalities are common in SLE with reported prevalences of between 5% and of 17%, reflecting differing methods of patient selection and assessments. The psychiatric syndromes in ACR Neuropsychiatric lupus Nomenclature Committee criteria include cognitive dysfunction, acute confusional state, anxiety disorder, mood disorders and psychosis [11].

SLE and other connective tissue diseases have rarely been reported among black Africans [12, 13] particularly West Africans [14]. Recent observations may however indicate otherwise [15]. Neuropsychiatric lupus has also been rarely reported among African blacks.

The objective of this study was to document the clinical presentation, laboratory findings and management of NPSLE in Nigerian patients and compare these with results of studies elsewhere.

Materials and methods

This is a retrospective study of SLE patients seen in a private rheumatology clinic, Arthrimed Specialist Clinic, Lagos, over a six year period between January 2001 and December 2006. . The clinic is located in Lagos, the commercial capital of Nigeria.

All cases of SLE seen were diagnosed based on American College of Rheumatology (ACR) criteria [16]. Classifications of the various neuropsychiatric syndromes were based on ACR nomenclature [17].

Results

A total of 64 cases of SLE were diagnosed during the study period, of which 33 subjects (51.6%) had at least one neuropsychiatric syndrome using the ACR nomenclature [17]. The demographic characteristics are as shown in Table 1.

Table 1: Demographic characteristics of 33 subjects with NPSLE

Female	31
Male	2
Age range	16-55 yrs (Mean 31.8 years, SD 11.5)
Duration of illness	4 months - 10 years (mean 3.2 years)

Majority of the subjects(13) presented with only one neuropsychiatric syndrome. Ten subjects had two coexisting syndromes. Three subjects each presented with three and four syndromes respectively while four patients had five coexisting neurological syndromes. Headache was the commonest presentation while dementia was the least.

Table 2: Frequency of the various NPSLE syndromes

NPSLE syndrome	Frequency (%)
Headache	22 (66.6)
Seizures	14 (42.4)
Psychosis	10 (30.3)
Cognitive impairment	8 (24.2)
Insomnia	7 (21.1)
Peripheral neuropathy	4 (12.2)
Mood disorders	6 (18.2)
Myelopathy	2 (6.1)
Cranial neuropathy (ptosis)	2 (6.1)
Dementia	1 (3.0)

Laboratory results

The erythrocyte sedimentation rate ranged between 26 to 160 with a mean of 95.5mm/hr. Seventeen subjects (51.5%) had ESR of 100mm/hour and above.

Anti-nuclear antibody (ANA)
All the subjects had ANA done and the titres and frequency are as shown in Table 3.

Table 3: Frequency and titres of ANA in 33 subjects

Titre	Frequency (%)
1:40	1 (3.1)
1:80	9 (27.2)
1:160	3 (9.1)
1:320	7 (21.3)
1:640	3 (9.1)
1:1280	6 (18.2)
Above 1:1280	4 (12.1)

Extractable nuclear antigen (ENA)
Twenty subjects had ENA serology. Of these, sixteen (80%) were positive while the remaining 4 (20%) were negative.

Anti – DNA
Twenty subjects had double stranded Anti DNA serology. Eleven (55%) had positive results while the remaining 9(45%) were negative.

Anti Cardiolipin Antibody (ACA)
Only two subjects both with myelopathy had ACA serology and both showed moderately elevated IgG Anti Cardiclipin antibody.

Table 4: Treatment regimens in 33 NPSLE patients

Treatment regimen	Number	%
IV Pulse mehtylprednisolone+IV Cyclophosphamide+prednisolone	12	36.3
Tab. Methotrexate+Prednisolone	10	30.3
Pulse Methylprednisolone+Azathioprine+ Prednisolone	9	27.3
Hydroxychloroquine +Prednisolone	2	6.1
All treatments	33	100

Treatment
The treatment regimens of the underlying SLE are as shown in Table 4. Fourteen subjects who had seizures were placed on Carbamazepine as most of the other anti-epileptics have been implicated in drug induced SLE. Subjects with headache were placed on paracetamol. All the patients were also placed on Aspirin 75 mg daily. Patients with psychosis were referred to the psychiatrists and were followed up in the clinic for the management of their lupus.

Outcome
At the end of six months, eighteen patients (54.5%) were better while five got worse and three died. However seven subjects (21%) were lost to follow up:

Discussion

Various nomenclatures have been used to define neurologic and psychiatric manifestations of SLE. These have been variously called Central Nervous System Vasculitis, CNS Lupus, neurolupus, lupus cerebritis. These nomenclatures are unsatisfactory and incomplete in their description. They have not quite highlighted the spectrum of the syndromes as related to the central, peripheral, autonomic systems as well as the psychiatric complement. The ACR ad Hoc Committee on Neuropsychiatric lupus has sought to clarify these issues by developing standardized nomenclature system for the 19 commonest NPSLE syndromes [17].

There have been various reports on the prevalences of NPSLE syndromes among SLE patients (Table 5). Our reported frequency of 51.6% is similar to that reported from United Kingdom [19]. The mean age at presentation on our study is 31 years which is not much different from other reports (Table 5). This is a reflection of the young age of SLE patients.

The predominance of females with NPSLE is a reflection of the female preponderance in SLE itself. Our study reveals a female to male ratio of 16.5:1.

Most of our patients presented with two or more neuropsychiatric syndromes This is in consonance with other studies [8,18]. Headache was the commonest presentation, being present in two-thirds of SLE patients (Table 3). This is similar to other reports from India and United Kingdom respectively [19,20] though only 4% was recorded in studies from Southern China. Seizures are common precautions of SLE and are usually isolated.

Certain clinical features at baseline are independent predictors of seizures and these include disease activity, particularly psychosis; moderate to high titre of serum anticardiolipin, anti Sm antibodies [9]. Many reports have indicated the relative high baseline disease activity among African-Americans. Other NPSLE syndromes such as psychosis, cognitive disorders, cranial neuropathy were seen in our study. Myelopathy was seen in two patients, both having moderately elevated IgG Anti cardiolipin Antibody. There have been reports of association of myelopathy with ACA among lupus patients[21,22].

Table 5: Comparative frequencies of NPSLE syndromes

NPSLE	Southern China Mok. *et. al.* (18)	India Robers *et.al* [20]	United Kingdom Sanna *et al.* [19]	Nigeria (Present study) Adelowo *et al.*
Number of NPSLE patients	96	39	185	33
Overall frequency (%)	19	78	57.3	51.6
Mean age	29.5	25.6	N/A	31.8
Headache (%)	4	55.6	24	66.6
Seizures (%)	28	20.5	8.3	42.4
Cognitive Disorders (%)	N/A	N/A	10.8	24.2
Psychosis (%)	11	16.2	7.7	30.3
Myelopathy (%)	8	N/A	N/A	6.1
Cranial Neuropathy (%)	3	N/A	N/A	6.1
Cerebrovascular Disease (%)	19	N/A	14.5	N/A
Acute confusional state (%)	14	N/A	3.7	18.2
Mood disorders (%)	6	16.7	N/A	18.2
Tremors (%)	N/A	20.5	N/A	N/A
Anxiety disorders (%)	1.5	N/A	7.4	N/A

NPSLE syndromes recorded in other studies were not seen.

These include cerebrovascular disease, mood disorders, acute confusional state and distal tremors (Table 5).The laboratory investigations have generally not been found to be helpful in discriminating the various NPSLE syndromes. Erythrocyte sedimentation Rate (ESR), Anti nuclear antibodies, are elevated in most SLE patients, with or without neuropsychiatric disorders. Our study confirms this. However, some other studies have shown that certain clinical features such as higher disease activity at baseline may be predictive of psychosis and cognitive impairment while presence of anti DNA was predictive of polyneuropathy Anti phospholipid antibodies were reported as being predictive of seizures and cerebro vascular diseases [10]. The ACR has recommended that SLE patients with focal neurologic manifestations should have anti phospholipid antibody determination. Limiting factors on our patients are the cost and the availability of serology tests. The pathogenesis of this condition is poorly understood, however it is hoped that antibodies to neuronal cell constituent, cytokines and other immunochemical phenomena may provide insights into potential mechanisms of the diseases [23]. These tests are however still investigational.

A major constraint in the diagnosis of NPSLE is absence of specific serological markers. In addition, findings in structural investigations studies such as CT, MRI, PET and neurophysiologic studies such as ECG and EMG may not be specific in diagnosis and are only useful in excluding other conditions that have similar presentation. Our study was only limited to the clinical features and serology. There was no CT or MRI done primarily because of the cost and its non availability.

The treatment of patients with the NPSLE in our study was not different from the standard treatment with immunosuppresives, steroids, anti-platelets and anti-epileptics when indicated. Low dose aspirin was given to all the patients because of the well recognized association of SLE with Anti phospholipid syndrome.The principle of management of NPSLE is the treatment of the underlying condition.The drug combination used was subject to the availability, since the appropriate drugs are not usually available. There have however been reports of association of neuropsychiatric lupus with the administrations of pulse methylprednisolone and

immunosuppressives [8, 24].Plasma exchange has also been found to be useful in the management of the manifestations of SLE including NPSLE [25]. More recently, B cells have shown to be important in the pathogenesis of SLE.

As a result, there has been development of monoclonal antibodies that effectively deplete B cells in human beings and target pathways essential for B cell and immune complex developments. Drugs that have been found effective and safe include Rituximab(anti CD 20);Epratuzumab(anti CD 22) and anti ds DNA toleragen-LJP 394 [26]. Other biologics at various stages of trials include monoclonal antibodies directed against Interleukins 6,18 as well as antibodies against Type 1 interferons. There is hope that early deployment of these agents will reduce the severity and incidence of NPSLE[27].

NPSLE are common features of SLE, a condition which itself is uncommonly reported in black Africans. The clinical and laboratory presentations are similar to these reported elsewhere though there may be differences in the relative frequencies of these syndromes. A high index of suspicion is required in the early diagnosis and management of these conditions

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Received: 20/01/08
Accepted: 27/01/09