Annals of Health Research
Volume 2, Issue No. 2
July - Dec. 2016

INVITED REVIEW ARTICLE

Connective Tissue Diseases: Challenges of management among Nigerians

Adelowo OO

Rheumatology Unit, Department of Medicine, Lagos State University Teaching Hospital, Ikeja.
President, African League of Association of Rheumatology
Chairman, Executive Committee of International League Against Rheumatism

Summary

Contrary to previous assumptions, Connective Tissue Diseases (CTD) are increasingly being reported among Africans, Nigerians inclusive. The clinical presentations are mostly similar to patterns described in other parts of the world, though with few differences. The management is patterned, as universally done, but drugs such as the biologics are infrequently used because of the prohibitive cost. The challenges of management arise mainly from a poor understanding of the spectrum, presentation and management of CTD as well as the non-affordability of the required drugs. The superstitious belief that these poorly-understood conditions are due to 'spiritual attacks' further compounds the problem of late presentation and sometimes accounts for the high morbidity and mortality. Continuing training of rheumatologists will enhance the understanding and management of rheumatological diseases.

Keywords: Arthritis, Challenges of management, Connective Tissue Diseases, Nigerians, Scleroderma, Systemic Lupus Erythematosus.

Introduction

Connective Tissue Diseases (CTD) are a group of autoimmune disorders characterised by the presence of anti-nuclear antibodies (ANA) in the blood of affected patients. ANA are a specific class of auto-antibodies that have the capability of attaching to and destroying structures within the cellular nuclei.CTD include conditions such as Systemic Lupus Erythematosus (the prototype of all CTDs), systemic sclerosis (Scleroderma), polymyositis, dermatomyositis and Sjogren syndrome. Apart from the presence of ANA and other antibodies, CTD are also characterised by multisystemic involvement, female preponderance, overlapping presentations, familial clustering, elevated acute phase reactants such as Erythrocytes Sedimentation Rate (ESR) and C-Reactive Protein (CRP) and good response to treatment with corticosteroids and immunosuppressive agents.

These diseases could also be classified as Systemic Autoimmune Diseases when other auto-immune diseases such as Rheumatoid arthritis, Vasculitis, Juvenile Idiopathic Arthritis and Mixed Connective Tissue Diseases are involved. CTD are found at various frequencies in different countries of the world. For instance, the estimated prevalence rates of SLE in North America, South America and Europe range from 1 to 23 per 100,000 people compared to 150 per 100, 000 in the USA. [1] However, the prevalence rates were higher among African-Americans and Hispanics. Unfortunately, there are no epidemiological studies of SLE among Africans hence, the non-availability of specific

Correspondence:
Prof. O.O. Adelowo
P. O. Box 7231,
Ikeja, Lagos
Email: femiadelowo2003@yahoo.com

population-based prevalence rates.

Systemic sclerosis has a far lesser frequency. In the USA, it occurs in 276 persons per million adults but to a lesser extent in Europe (80 – 150 per million adults). [2], [3] There are no epidemiological data on systemic sclerosis from Africa, although it has mostly been reported in South Africa [4] and in Nigeria. [5] Inflammatory myopathies, polymyositis and dermatomyositis are rare disorders with an annual incidence of 2 to 7 cases per million persons. [6]

Sjogren's syndrome is a connective tissue disease affecting the exocrine glands and resulting in dryness of main mucosal surfaces such as the mouth, eyes, nose, pharynx, larynx and vagina. This condition affects mostly middle-aged women but may also affect children, men and the elderly. The extra-glandular (systemic) affectation may result in increased morbidity and mortality. The main features of the syndrome include dry mouth and dry eyes while the systemic features may include bronchiectasis, chronic obstructive airway disease, glomerulonephritis, renal tubular acidosis, purpura, annular erythema, pericarditis and non-erosive arthritis.

Defined associations of Connective Tissue Diseases

Mixed Connective Tissue Diseases: Though disputably recognised as a distinct disease entity, this condition is characterised by the presence of clinical features of SLE, systemic sclerosis and polymyositis. It is characterised serologically, by the presence of high titres of Anti UI – RNP autoantibodies.

Overlap Syndromes: These are characterised by a combination of at least two connective tissue diseases occurring in the same patient or an overlap of one connective tissue disease and inflammatory arthritis such as rheumatoid arthritis. The major features of one connective tissue disease usually also occur with another connective tissue disease. Such overlaps can involve systemic sclerosis and inflammatory myopathies or systemic sclerosis and SLE. It may also include SLE and rheumatoid arthritis, and this is known as Rhupus.

Undifferentiated Connective Tissue Disease: Individuals who have features of a connective tissue disease but without fulfilling the stipulated diagnostic criteria of a particular connective tissue disease are classified as undifferentiated. This condition is regarded as a connective tissue disease in evolution. Affected individuals characteristically present with Raynaud's phenomenon and also multiple clinical and serological features of rheumatic diseases which do not allow the diagnosis of a specific entity.

Are these conditions rare in Nigerian and do they differ from elsewhere?

Connective Tissue Diseases are rarely reported among African blacks. Various theories and hypotheses have been proposed to explain this observation among African blacks. Symmons [7] had even proposed a gradient theory suggesting that the prevalence of SLE, for instance, increases from the southern part to the northern part of Africa and higher across the Mediterranean and further into Europe. Butcher [8] also postulated that the malaria endemicity in Sub - Saharan Africa inhibits the occurrence of auto–immune diseases such as SLE and sarcoidosis. Other reports have also indicated that rheumatoid arthritis, though not strictly a connective tissue disease, is rare among West Africans. [9],[10] also, reports from East Africa have also suggested the rarity of CTD. [11] However, the preceding may not be entirely accurate as recent reports have indicated that CTD may not be rare among black Africans as previously known. [12]-[16]

Clinical Presentations

Rheumatoid Arthritis (RA)

Although this disease condition is an inflammatory arthritis, the clinical presentations and management protocol for RA are similar to those of CTD as a whole. The condition presents with symmetrical polyarthritis, joint morning stiffness and constitutional features. It typically affects any age group but mostly, middle age females. It affects mainly the synovial tissue of small joints of the hand and feet as well as the

large joints of the knees, shoulders, elbows and the hip. It is an auto-immune condition with inflammatory changes mostly affecting the peripheral symmetrical joints but sparing the spine. However, the inflammatory changes can also affect other organ systems such as the lungs, eyes, heart and the reticuloendothelial system but rarely, the kidneys. Without treatment, it can lead to joint deformities and can be associated with increased cardiovascular morbidities and mortality.

There have been few population studies among black Africans. The reports from South Africa have demonstrated a low prevalence and milder clinical course of RA compared to the findings among the Caucasians. Isolated reports from West Africa have also suggested the rarity of the condition. [9], [10] However, recent reports from Nigeria have indicated otherwise. A report from Nigeria described RA among 200 patients attending a Rheumatology Clinic. [16] Undocumented reports from Rheumatology Clinics in hospitals across Nigeria have also indicated that RA is not rare, though uncommon. A yet-to-be published study from a private Rheumatology Clinic in Lagos, Nigeria found a frequency of 13.2% among 4000 patients registered in that clinic. [17] It may be attractive to hypothesise that the prevalence of RA is low in the rural communities compared to the urban centres. This observation, thus, raises the possibility of causal roles of environmental factors in RA.

Systemic Lupus Erythematosus (SLE)

SLE is a multi-systemic autoimmune disease characterised by a mixture of acute and chronic inflammatory processes affecting any and every organ in the body. SLE, also called Lupus, affects mainly females of childbearing age (F: M = 9: 1). It has a particular predilection for the skin, joints, serous membranes, lungs, and the heart. The prognosis in SLE is mainly determined by the affectation of the kidneys and the central nervous system. One of its complications, the Anti-Phospholipid Syndrome, is a well-recognized cause of recurrent pregnancy losses, pre–eclampsia, intrauterine growth restriction and small for age babies.

Similar to other systemic auto-immune diseases, SLE is rare among black Africans. However, there have been increasing reports of the condition in recent times. [18] - [20] A visit to any rheumatology clinic or medical ward, especially in the urban centres, will suggest that SLE is almost assuming epidemic proportions. The common presentations of SLE among Nigerians include recurrent fever, polyarthralgia, fatigue and loss of weight; a constellation of symptoms often wrongly attributed to malaria or typhoid fever. Other common manifestations of this condition among Nigerians include mouth ulcers, skin rashes, and loss of hair. [20] Many times, because of the low level of awareness of the general populace concerning this condition, patients and relations alike often misinterpret the symptoms of this condition and wrongly give the illness a spiritual or supernatural connotation.

SLE is a hydra-headed, chameleonic disease which may first present as a renal disease, often with dire consequences. [21] Although it affects females of childbearing age more frequently, it may also occur among children aged 16 years or less – a condition named Juvenile SLE. Also, SLE may present with significant neuropsychiatric features. [22] Various autoantibodies have been reported in SLE, and they are of diagnostic, prognostic and monitoring significance. [23]

In a few instances, SLE may have some unusual presentations such as SLE-associated vasculitis resulting in digital gangrene as reported from Nigeria. [24] A recent audit of the 4000 rheumatological cases seen in a private clinic in Lagos showed SLE in only 215 (5.4%) of patients. Out of the cases seen, Juvenile SLE was recorded among only three children. [17]

Inflammatory Myopathies

This is an uncommon connective tissue disease affecting the muscles – both striated and smooth. There are three major types of inflammatory myopathies: polymyositis, dermatomyositis and inclusion body myositis. The first two sub-types affect mainly proximal skeletal muscles while the third sub-type affects distal muscles. The clinical features are primarily those of proximal muscle weakness resulting in difficulty with combing the hair, tying head gears, getting up

from sitting position and ascending the staircase. In dermatomyositis, the skin is also affected, and this is characterised by lesions such as Heliotrope rashes, photosensitive erythematous rashes and Gottron's lesions. Other cutaneous presentations include the Shawl sign and mechanic hand.

The diagnosis of inflammatory myopathies is based on the Bohan and Peter's criteria. The inflammatory myopathies have been reported among Nigerians [25], and a report of dermatomyositis in a Nigerian child was the first from Africa. [26] An audit of rheumatological cases seen in a private clinic showed the frequency of dermatomyositis to be 0.8%. [17] Inflammatory myopathies may also be associated with cardiac conditions such as arrhythmias, heart block, cardiomyopathy and ischaemic heart diseases. Gastrointestinal manifestations include reflux oesophagitis, constipation and malabsorption syndrome. The involvement of the lungs manifests with interstitial pneumonitis and pleural effusion.

Systemic Sclerosis (Scleroderma)

This is a rare connective tissue disease globally. It affects the skin essentially, but it may also affect the kidneys, lungs, heart and the gastrointestinal tract. Only a few cases of scleroderma have been reported among Nigerians. [27] The pathogenesis is centred around immune dysregulation endothelial dysfunction and excessive fibrous tissue deposition in the skin and internal organs. There are two major types of scleroderma – the diffuse type and the limited type. Due to the affectation of the vasculature, it may present with Raynaud's phenomenon, digital ischaemia and auto-amputation. The involvement of the pulmonary vasculature results in pulmonary hypertension and pulmonary fibrosis.

Sjogren's syndrome

This condition affects the salivary glands and the secretory structures of the eyes. Therefore, it results in dry mouth and dry eyes. It also affects the skin, lungs, gastro–intestinal system and the kidneys. It also manifests with lymphoma when the disease affects the reticuloendothelial system. This disease condition has not been frequently reported among Nigerians as a recent audit identified only two cases out of 4000 patients with rheumatological conditions. [17]

Antiphospholipid syndrome (APS)

APS may occur as a primary condition, or it may be secondary to other CTD such as SLE, scleroderma and inflammatory myopathies. The condition is characterised by recurrent venous or arterial thrombosis, recurrent pregnancy losses (usually mid-trimester), pre-eclampsia, intra-uterine growth restriction and delivery of small-for-age babies. This condition is being increasingly recognised as an important cause of pregnancy losses. Serological investigations are deployed to make the diagnosis in such instances of recurrent pregnancy losses. There have been only a few reports of APS from Nigeria. [28], [29] Only six cases were identified in the audit of a population of 4000 patients in a Rheumatology Clinic. This suggests the rarity of APS among Nigerians. Nevertheless, it is desirable that gynaecologists involved in the care of women with recurrent pregnancy losses must carry out the appropriate serological tests for APS.

Challenges in the management of Connective Tissue Diseases in Nigeria

It appears the major challenge in the management of CTD in Nigeria is the low awareness and ignorance on the part of the people affected and their relations. Due to the variable presentation and the poor understanding of the conditions, many people attribute the conditions to metaphysical causes. This is compounded by the fact that, in the course of the diseases, the symptoms tend to evolve one into the other such that, no sooner is one symptom gotten over than another one surfaces. This may be all confusing to the individuals affected by the disease, their relations and even the attending doctors.

Another challenge is the poor understanding of CTD among many physicians. These conditions are often not taught in details in most Nigerian medical schools. Even when taught, more emphasis is placed on the complications rather than the underlying disease entities; for example, the presence of joint deformities is emphasized in

rheumatoid arthritis or the mistaken belief that SLE is only characterised by the presence of malar rashes. Many doctors miss the diagnosis of SLE because of its protean mode of presentation. Often, SLE is repeatedly misdiagnosed as malaria or Typhoid fever. Such frustration occasionally misleads some doctors into suggesting metaphysical explanations for such illnesses.

The dearth of expertise in the subspecialty of rheumatology in the country is another major challenge. For several years, there was only one Teaching Hospital offering rheumatological care services along with one private clinic. However, the situation has now improved considerably, and a minimum of thirty doctors are either still in sub-specialty training in rheumatology or have completed the training and are practising rheumatology. Although rheumatology units are increasing in number across the Nigerian landscape, the distribution is still insufficient for the country with a population of about 170 million.

The high cost of care is another major challenge. Rheumatological diseases are often chronic and expensive to manage; therefore, both the direct and indirect costs can be so overwhelming. Expenses will include the cost of drugs (which are mostly expensive), laboratory investigations, imaging studies and support care such as physiotherapy. The indirect costs include transportation for hospital appointments, loss of income and disability costs. For instance, more than half of the patients with rheumatoid arthritis would have lost their jobs within five years of untreated RA. Poor clinic attendance and high rate of default from out-patient care are additional challenges. Individuals affected by CTD expect an instant cure, but when confronted with the gloomy details of prognostic assessment, the usual response is to seek alternative care, either spiritual or metaphysical, where a cure is usually promised. Expectedly, valuable time is lost, and complications ensue in such instances.

Of prime importance is the non- availability of drugs required for the treatment of the disorders such as the disease-modifying anti– rheumatic drugs (DMARDs) and Biologics (which have made a substantial change to the quality of life in CTD). Biologics are very expensive and not always available in the country. The only two agents which are presently readily available include Rituximab (Mabthera®) and Etanercept (Enbrel®). Since the patients pay out of pocket for their care, the drugs are not affordable. In addition, the Health Maintenance Organizations (HMO) usually refuse to pay for such expensive items.

Conclusion

Although they are infrequently encountered in practice in the Nigerian setting, CTD are associated with high morbidities and mortality arising from the protean nature of the manifestations, the chronic course of the illness, the high cost of care in a developing economy like Nigeria and poor pattern of appropriate health care seeking behaviour. It is believed that as more rheumatology units are set up across the country and as doctors have heightened awareness and knowledge of CTD, especially through formal schematic training, the morbidities and mortality associated with the disorders would be greatly reduced in Nigeria.

Conflict of Interest: None.
Funding: Not required
Publication History: Submitted: 06 September 2016; Accepted: 08 November 2016.

References

1. Tocounidou C, Bertsias G, Gordon C et al. Systemic Lupus Erythematosus: Pathogenesis and Clinical Features. In: Bijlsma JWJ, Hachulla E (Eds) EULAR Textbook on Rheumatic Diseases. London: BMJ Publishing Group: 2015.
2. Medsger TA Jr, Masi AT. Epidemiology of Systemic Sclerosis. Ann Intern Med 1973: 74; 714 – 721.
3. Mayes MD, Lacey JV Jr, Beebe–Dimmer J,

Gillespie BW, Cooper B, Laing TJ, *et al*. Prevalence, Incidence, Survival and Disease Characteristics of Systemic Sclerosis in a large US Population. Arthritis Rheum 2003; 48: 2246 – 2255.

4. Tager RE, Tikly M. Clinical and laboratory manifestations of Systemic Sclerosis (Scleroderma) in Black South Africans. Rheumatol (Oxford) 1999; 38(5): 397 – 400.
5. Adelowo OO, Oguntona S. Scleroderma (Systemic Sclerosis) among Nigerians. Clin Rheumatol 2009; 28: 1121 – 1125.
6. Iaccarino L, Cooper RG, Doria A. Polymyositis and Dermatomyositis. In: Bijlsma JWJ, Hachulla E.(Eds) EULAR Textbook on Rheumatic Diseases. London, BMJ Publishing Group: 2015.
7. Symmons DP. Frequency of Lupus in People of African Origin. Lupus; 1995; 4: 176 – 178.
8. Butcher GA. Malaria and macrophage functions in Africans: a possible link with auto-immune disease? Med Hypotheses 1996; 47: 97–100.
9. Adebajo A, Davis P. Rheumatic diseases in African blacks. Semin Arthritis Rheum 1994: 24: 139 – 153.
10. Silman AJ, Oller W, Holligan S, Birrell F, Adebajo A, Asuzu MC, *et al*. Absence of Rheumatoid Arthritis in a rural Nigerian population. J Rheumatol 1993; 20: 618 – 622.
11. Mc Gill PE, Oyoo GO. Rheumatic disorders in Sub-Saharan Africa. East Afr Med J 2002; 79: 214 – 216.
12. Ouedraogo DD, Singbo J, Diallo O, Sawadogo SA *et al*. Rheumatoid Arthritis in Burkina Faso: Clinical and Serological Profiles. Clin Rheumatol 2011: 30: 1617 – 1621.
13. Njovbu, PD, Trollips S, Chipeta T *et al*. Clinical and diagnostic features of Systemic Lupus Erythematosus (SLE) in Zambians. Abstract P3. AFLAR and SARAA Congress. Durban, South Africa. 2013.
14. Ekwom PE. Systemic Lupus Erythematosus (SLE) at the Kenyatta National Hospital. Clin Rheumatol 2013: 32: 1215 – 1217.
15. Adelowo OO, Bello MKN. Systemic Auto-immune diseases: Not so rare in Black Africans. Rheumatol Current Res 2014; 4: 1.
16. Adelowo OO, Ojo O, Oduenyi I, Okwara CC. Rheumatoid Arthritis among Nigerians: the first 200 patients from a Rheumatology Clinic. Clin Rheumatol 2010; 29: 593 – 597.
17. Adelowo OO, Ojo O, Oguntona S, Emorinkhen A. Spectrum of Rheumatological diseases in a private practice clinic in Nigeria – In press
18. Dessein PH, Gledhill RF, Rossoun DS, Systemic Lupus Erythematosus in black south Africans. S Afr Med J 1988; 74: 387 – 389.
19. Tickly M, Navarra SV. Lupus in the developing world – is it any different? Best Pract Res Clin Rheumatol 2008; 22: 643 – 655.
20. Adelowo OO, Oguntona SA. Pattern of Systemic Lupus Erythematosus among Nigerians. Clin Rheumatol 2009; 28: 699 – 703.
21. Adelowo OO, Umezurike T, Awobusuyi J, Olaosebikan H. Nephritis as initial diagnosis in Nigerian lupus patients. Afr J Med Med Sci 2014; 43(2): 99 – 105.
22. Adelowo OO, Oguntona AS, Ojo O. Neuropsychiatric Systemic Lupus Erythematosus among Nigerians. Afr J Med. Med Sci 2009; 38: 33- 38.
23. Adelowo OO, Ojo O, Oduenyi I. Auto-antibodies in Nigerian lupus patients. Afr J Med Med Sci 2012; 41(2): 177 – 181.
24. Adelowo OO, Olaosebikan H, Ajani H, Omosebi DT. Digital gangrene as the initial presentation of systemic lupus erythematosus. BMJ Case Reports 2012; doi: 10.1136/bcr-2012-006259.
25. Adelowo OO, Edomwonyi U, Olaosebikan H. Inflammatory myopathies in Nigerians: Case series and literature review. Afri J Med Med Sci 2013; 42(2): 143 – 149.
26. Adelowo OO, Nwankwo M, Olaosebikan H. Juvenile Dermatomyositis in a Nigerian child. BMJ Case Report 2014; doi: 10.1136/bcr-2013-201232.
27. Adelowo OO, Oguntona S. Scleroderma (Systemic Sclerosis) among Nigerians. Clin Rheumatol 2009; 28: 1121 – 1125.
28. Adelowo OO, Oguntona S. Antiphospholipid Syndrome: Report of Five Cases. East Afr Med J 2009; 86(2); 517 – 519.
29. Adelowo OO, Adetoro OO. Recurrent pregnancy loss and antiphospholipid syndrome: an overlooked association. Afr J Med Med Sci 2010; 39: 227 – 231.