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Gene therapy and rheumatic diseases: Back to the future

Gene therapy has become a major field in modern biotechnology, especially in the area of human health. Fascinating developments achieved in the past decades are impressive examples of an interdisciplinary interplay between medicine, biology and engineering. Gene therapy opens up challenging new areas. The consequences of wealth in genetic knowledge for the practice of medicine are profound with the most significant impact being the enhancement of our understanding of disease etiology and pathogenesis. However, genetics is rapidly playing a more prominent role in the diagnosis, prevention and treatment of disease.

Gene therapy concepts have been extensively developed and tested in clinical trials in many diseases including cancer and Rheumatoid Arthritis (RA). In a broader sense, gene therapy can be considered not only the replacement of a defective endogenous gene, but can also incorporate the addition of foreign or modified genes to alter a biological function. It is noteworthy that the ability to transfer genes efficiently and safely to target cells is central to any successful gene therapy.

It consists of repairing or replacing mutated genes. Gene therapy also regulates the expression of genes, affects the immune system and directs the cell to be destroyed. With it, the basics of the disease can also be learnt, the diagnosis improved or a form of therapy established, plus the results of treatment can be tracked. It gives great hope for an effective fight against many diseases. Over time and with proper oversight, gene therapy might become an effective weapon in modern medicine’s arsenal to help fight diseases such as AIDS, diabetes, high blood pressure, coronary heart disease, peripheral vascular disease, neurodegenerative diseases, hemophilia and other genetic disorders as well as many rheumatic and connective tissue diseases.

Gene therapy is performed ex vivo, when a gene is introduced into the cells outside the body. These cells are then introduced into the host, where the desired protein is subjected to expression. The in vivo method is the direct injection of the gene into the body. A gene vector is used and its type depends on the delivered gene or its destination. The recombinant vector, with a new piece of DNA, is inserted into the patient or directly into tissue or cells. Most of the vectors used in gene therapy are viruses, and these are both those with DNA, as well as those with RNA. The viruses used as gene therapy vectors include retroviruses, AAV (adenoassociated virus), adenoviruses, HSV (herpes simplex virus), other lentiviruses, the cytomegalovirus (CMV) and influenza virus. Viruses were the first to be used in gene therapy because of their ability in introducing DNA into the targeted cells. However, for this method they have been changed so that they do not have the ability to replicate. The genes responsible for the expression of proteins harmful to the host are also removed, and the fragments meant for therapeutic use are implemented. Thus prepared, the virus is a safe vector.

Gene transfer using a viral vector is known as transduction. In viral delivery systems, nonpathogenic attenuated viruses can be used as delivery systems for genes/DNA molecules; especially plasmids. Because of their ability to...
sneak into cells, viruses appear to be efficient delivery vehicles for replacing mutant genes. The viral genes for infection are taken out and then the therapeutic gene is inserted into the viral chromosome. The hybrid is then mixed with purified viral capsid proteins. Viruses have the capacity to carry foreign genes and efficiently deliver them with competent gene expression. Because these vector systems have unique advantages and limitations, each has applications for which it is best suited. Gene expression using viral vectors has been achieved with high transfection efficiencies in tissues such as kidney, heart muscle, eye and ovary.

Due to extra safety concerns, immunogenicity and production issues associated with viral vectors, non-viral delivery systems were developed by concatenating of genes (DNA) to various chemical formulations. Non-viral gene transfer is known as transfection. The need for safer alternatives has led to the development of liposomes, cationic polyplexes, micro and nanoparticles. Although these alternative vectors have shown promise, degradable nanoparticles are the only non-viral vectors that can provide a targeted intracellular delivery with controlled release properties.

In rheumatic diseases, concerns of using biologically-derived immunomodulating compounds such as TNF-α inhibitors, IL-1 blocking agents and anti-inflammatory cytokines include the re-activation of granulomatous diseases especially tuberculosis, re-activation of chronic hepatitis B if not given concurrently with antiviral therapy and increased lymphoma risk. An alternative approach might be the use of gene transfer to deliver therapeutic genes locally at the site of inflammation. Gene therapy emerged as a novel successful anti-arthritis strategy as a part of the wider movement toward biologic therapy. Continuous identification of specific targets and candidate genes together with refined approaches offers new promises for the future of gene therapy design in rheumatic diseases.

A number of different types of transgenes have been suggested for local therapy of diseased joints including those encoding cytokine antagonists, immunomodulators, antiangiogenic factors, apoptotic agents, antioxidants, and inhibitors of mitosis as well as molecules that modulate cell signaling and the activities of transcription factors. However, future studies will need to address improving targeted delivery of vectors, regulating and obtaining long-term transgene expression and improving the safety and efficacy of the vectors already in use before being available for arthritis.

In previous studies, gene polymorphism in RA and Systemic Lupus Erythematosus (SLE) has been confirmed. Interest in applying gene therapy to the treatment of rheumatic diseases began in the early 1990s with attempts to deliver DNAs to the synovial lining of joints. Because Sjögren syndrome and SLE, unlike RA, do not respond well to present biologies, alternative approaches, such as gene therapy, seem worthwhile. Their success could encourage further investigations in serious intractable rheumatic diseases, such as scleroderma. Amazing advances have been made in our understanding of the genetic basis of human SLE and gene therapy in lupus promises to correct the aberrant immunological response without the numerous side effects of the immunosuppressant medications. However, undesirable side effects such as the impaired response to T-cell-dependant and independent antigens, increased susceptibility for infectious diseases have been indicated. Thus, despite its promise, gene therapy is a young field and a variety of questions must be addressed in lupus.

Heritability of serum uric acid concentration is high, suggesting that genetic variation might contribute to determining its concentration through regulation of synthesis, excretion, or reabsorption. Knowledge of genotype could help to identify individuals at risk of developing gout long before the onset of clinical features. In addition to risk prediction, knowledge of an individual’s genotype could be used to help guide clinical decisions, especially with respect to selection of drugs that are known to increase uric acid concentration and worsen gout. Acute gout is Monosodium Urate (MSU) crystal–induced acute inflammation that is characterized by a massive influx of neutrophils into the inflamed joints. The deposition of MSU crystals rapidly induces the production of cytokines and chemokines, which then play an important role in the development of acute inflammation in gouty arthritis. IL-10 gene therapy can block the production of cytokines and chemokines by MSU crystal–stimulated macrophages in vitro and ameliorate MSU crystal–induced acute inflammation in vivo.

It is becoming clear that many genes, each with a small effect size, contribute to the risk of developing osteoarthritis (OA). However, the genetics of OA pain are only just starting to be explored. OA was relatively late to enter the Genome-Wide Association Scans (GWAS) era but the returns were substantial. Gene products triggering anti-inflammatory or chondroprotective effects are of obvious therapeutic utility. As OA affects a limited number of weight-bearing joints and has no major extra-articular manifestations, it is well suited to local, intra-articular gene therapy. The efficacy of local gene delivery in OA treatment has been confirmed using interleukin-1 receptor antagonist (IL-1Ra) as the transgene product; thus reflecting the importance of IL-1 as a mediator in the osteoarthritic joint.

Many signal transduction pathways involved in joint formation are stimulated by Bone Morphogenetic Proteins (BMPs), Transforming Growth Factors (TGFs) and Wnt family proteins, and components of each of these pathways have been implicated in OA.

The future outlook for genetics of rheumatic diseases appears likely to be shaped by larger meta-analytical efforts to identify additional susceptibility loci. Gene therapy is a rapidly growing field of medicine.
and actually a sophisticated extension of conventional medical therapy. Rather than treating the patient’s disease with drugs or surgery, the patient receives DNA. It may hold the cure for many of the rheumatic diseases.

**References**

Abstract

Background: Scleroderma is a chronic multisystem autoimmune disease of unknown aetiology. Scleroderma is characterized by widespread obliteratorive vasculopathy of small arteries and is associated with varying degrees of tissue fibrosis and multiple organ involvement. Pulmonary disease is an important component of SSc. It is estimated that 80% of patients with SSc have some evidence of pulmonary disease. Systemic sclerosis has the poorest prognosis amongst rheumatology diseases with the highest case-specific mortality of any of the autoimmune rheumatic diseases as well as causing major morbidity.

Objective: This article will review pathogenesis, diagnosis and management of pulmonary disease in scleroderma.

Data source: Literature review of relevant published literature from both Africa and the rest of the world.

Data synthesis: The pathogenesis of lung disease in scleroderma involves a variety of pathways, including immunological/inflammatory activation and vascular injury. The primary cytokines responsible for the disease are unknown but it is postulated that it involves a complex interplay between inflammatory, B lymphocyte antibody production, oxidative stress and fibrotic pathways. This leads to the activation of lung fibroblasts by inflammatory and fibrotic mediators. Lung fibroblasts play a central role in the deposition of excess intracellular matrix. This inflammatory response leads to fibrosis and occurs in the setting of vascular derangements. The most common symptoms are dry cough and dyspnea on exertion. The high morbidity and mortality seen in SSc is generally attributed to the two major pulmonary manifestations of the disease: interstitial pulmonary fibrosis, or interstitial lung disease, and pulmonary arterial hypertension. Exertional dyspnea and dry cough are the most common presenting symptoms in patients with SSc who develop pulmonary involvement. Algorithm of diagnostic procedures in these patients does not differ considerably from the procedures of any other interstitial lung disease. At the current time, cyclophosphamide remains the best studied therapeutic agent although alternatives are actively being evaluated. The pathogenesis of pulmonary disease in scleroderma is still an enigma and is being actively researched. This will advance our understanding of the disease and ability to care for these patients.

Conclusion: Pulmonary complications are common in SSc and are the leading causes of death. Careful evaluation by the clinician is warranted to detect the presence of an ILD and to select patients appropriately for consideration of therapy. It is a major clinical challenge largely due to the enigma of the disease pathology as well as limited therapeutic options available. This is compounded by the perceived lack of evidence for clinical effectiveness of those treatments that are currently in use. Clinical trials are underway and offer hope for novel approaches to this mysterious and often devastating manifestation of scleroderma.

Introduction

Scleroderma is a chronic systemic disease of unknown aetiology. It affects around 15 persons in one million inhabitants in all parts of the world. The most affected are frequently women aged between 40–60 years. Previously reported incidence and prevalence estimates vary greatly according to geographic location and methods of case ascertainment. Classification criteria were not developed until 1980 when the American Rheumatism Association (now the American College of Rheumatology, ACR) proposed criteria to distinguish SSc from other connective tissue diseases. The exact prevalence in Africa is not known. Scleroderma can affect many organs in the body, including the lungs, although not everyone will experience the symptoms of lung disease. Scleroderma is divided into limited and diffuse based on the extent of skin involvement. Limited cutaneous involves the forearms, hands, legs, feet and face. Diffuse cutaneous can involve any body...
area. Both will involve internal organs, differentiating them from the localized form. The last major category, Sine, is rare and involves only internal organs, sparing the skin. The major mortality and much of the morbidity of scleroderma arises through the development of specific complications of the disease including organ based complications such as cardiopulmonary, renal or gastrointestinal manifestations. The frequency and diverse nature of these complications makes systematic assessment and long term follow up essential to good management of scleroderma. Pulmonary involvement occurs in at least two thirds of systemic sclerosis patients and about 10-15% of them will develop severe lung disease during the course of their illness. Pulmonary disease has surpassed renal disease and is now the leading cause of death amongst patients with scleroderma. The estimated mortality of pulmonary disease from all causes is said to be 33%2. This makes pulmonary disease second only to esophageal disease as the most commonly seen visceral component. Moreover, pulmonary involvement has a poorer prognosis. The pulmonary complications are Interstitial Lung Disease (ILD) or pulmonary fibrosis and Pulmonary Arterial Hypertension (PAH). Median survival in scleroderma patients with pulmonary hypertension ranges between 1 and 3 years4. In subjects with severe progressive pulmonary fibrosis the mean survival is less than 3 years5. PAH can occur as an isolated form, in progressive pulmonary fibrosis the mean survival is less than 3 years6. PAH has a poorer prognosis. The pulmonary complications are Interstitial Lung Disease (ILD) or pulmonary fibrosis and PAH. Median survival in scleroderma patients with pulmonary hypertension ranges between 1 and 3 years4. In subjects with severe progressive pulmonary fibrosis the mean survival is less than 3 years5. PAH can occur as an isolated form, in progressive pulmonary fibrosis the mean survival is less than 3 years6. PAH has a poorer prognosis.

Pathogenesis

The pathogenesis of SSc-ILD involves a variety of abnormalities, including immunological/inflammatory activation and vascular injury. The primary cytokines responsible for the disease are unknown but it is thought that it involves a complex interplay between inflammatory cytokines, B lymphocyte antibody production, oxidative stress and fibrotic pathways leading to the deposition of excess intracellular matrix12. Lung fibroblasts play a central role as they are activated and produce extracellular matrix as well as many of the inflammatory and fibrotic mediators. This inflammatory response leads to fibrosis and occurs in the setting of vascular derangements13. Although the precise sequence of events is unclear, chronic inflammation, possibly in response to an unknown injury, is believed to play a significant role in the fibrotic process. This contrasts with idiopathic pulmonary fibrosis, where the hypothesis of inflammation preceding fibrosis has been largely abandoned, not least because anti-inflammatory and immunosuppressive agents are largely ineffective14. Humoral and immune cell abnormalities are found in SSc, including the presence of autoantibodies specific to the disease, chronic mononuclear cell infiltration of affected tissues, and dysregulation of lymphokine and growth factor production15,16. In SSc-ILD, studies on bronchoalveolar lavage have shown a gene expression signature consistent with increased expression of chemokine and chemokine receptor genes involved in the recruitment of T cells and chronic macrophage activation, with CD8+ T cells mainly expressing pro-fibrotic Th2 cytokines IL-4 and IL-5. Proteomic analysis confirms the predominant Th2 cytokine profile in SSc bronchoalveolar lavage fluid17. Patients with systemic sclerosis express a variety of disease-specific autoantibodies, mostly mutually exclusive and associated with different subsets of the disease. The autoantibodies classically associated with SSC and most frequently found are anti-topoisomerase (ATA, also known as Scl-70), anti-centromere (ACA) and anti RNA polymerase I/III (ARA). Other disease-specific auto antibodies which occur less commonly include anti- Th/To, anti U3- RNP and anti-PM/Scl autoantibodies, associated with polymyositis/scleroderma overlap18. None SSc-specific autoantibodies include anti-Ro (SS-A) and anti-La (SS-B), most often found in systemic lupus erythematosus and Sjogren’s syndrome, anti- RNA polymerase II, also found in SLE and overlap syndromes, anti-Sm antibodies usually found in SLE, and anti U1-RNP associated with what was previously termed “mixed connective tissue disease”. Whether these autoantibodies play a direct pathogenetic role or are simply epiphenomena is unknown. However, they have clear clinical utility as markers of different subsets of disease with characteristic patterns of organ involvement, and, as mentioned later, may well identify genetic subsets of the disease. The two main types of lung involvement, ILD or isolated pulmonary hypertension, are very tightly associated with specific auto-antibodies.

Antitopoisomerase Antibodies (ATA), present in approximately 20% of patients, are strongly linked to the development of lung fibrosis. Roughly half of SSc
patients in whom pulmonary fibrosis develops have ATA antibodies; conversely, most patients (>85%) with ATA positivity have pulmonary fibrosis. Some studies, but not all, suggest that ATA is also predictive of higher rates of progression of lung fibrosis. The less frequent anti-nuclear antibodies, anti-U3 RNP antibody and anti TH/To, are also associated with an increased risk of pulmonary disease; the latter also seem to be associated with development of pulmonary hypertension disproportionate to the degree of interstitial involvement. Interestingly, anti TH/To have also been described in a subgroup of patients with clinical idiopathic pulmonary fibrosis and a UIP pattern on histology; the prognosis of these patients did not differ from those with IPF but no autoantibodies, lending support to the suggestion that Th/To autoantibodies may be markers of aggressive lung disease. Microvascular injury is believed to be the earliest and possibly the primary event in the pathogenesis of SSc. Outside of the lungs, Raynaud’s phenomenon precedes the onset of skin fibrosis often by several years in most patients. In the lungs, a study of post-mortem lung tissue identified excessive formation of irregularly shaped alveolar capillaries with an increase in the number of endothelial cells in the early stages of lung fibrosis. Although vascular abnormalities almost certainly precede fibrosis, the sequence of events and interplay with autoimmunity is not at all clear. It has been suggested that microvascular injury induces inflammation and autoimmunity, which in turn have direct and indirect roles in inducing fibroblast activation, a key event in the development of fibrosis. Fibroblasts are the main cell type responsible for the excessive extracellular matrix synthesis and deposition seen in fibrosing lung disorders. Fibroblasts can differentiate into a more metabolically active cell with features intermediate between fibroblasts and smooth muscle cells, termed myofibroblast. Myofibroblasts express high levels of α-smooth muscle actin and synthesize increased levels of collagens, TIMP and other ECM components in vitro. Fibroblasts explanted from SSc-ILD lungs have been shown to be phenotypically different from control lung fibroblasts, although there is a degree of heterogeneity in this cell population. SSc fibroblasts are considered to be in an activated state and the proportion of alpha-smooth muscle actin positive cells is elevated in cultures of SSc fibroblasts. An intriguing question regards the origin of the stimulated fibroblasts; traditionally, they were believed to derive from the activation of resident fibroblasts induced by in situ cytokines and growth factors. However, accumulating evidence suggests that in fibrotic lung disease, interstitial lung fibroblasts can derive from at least two additional sources, the trans-differentiation of epithelial cells into myofibroblasts, and from a circulating fibroblast-like cell, the fibrocyte, derived from bone marrow stem cells, in response to cytokines and chemokines produced at the site of lung injury/inflammation. It is possible that all three mechanisms are operating in SSc-ILD, although the relative contribution of each cell type has yet to be delineated. It is unclear what environmental or genetic factors may contribute to the development of ILD in SSc. While environmental triggers have been postulated in the pathophysiology of SSc in general and environmental exposures such as polyvinylchloride and an impurity in one preparation of L-tryptophan have been known to trigger scleroderma like syndromes, there has never been a clearly established environmental link. Moreover, there has never been an environmental exposure implicated specific to ILD associated with SSc. Evidence suggests that gastroesophageal reflux may contribute to the onset or progression of the disease, although the exact role of this reflux remains poorly understood. A genetic contribution to scleroderma is supported by observed familial aggregation, ethnic predispositions, gene association studies and genome wide studies. Pedigrees have been described that demonstrate members with SSC as well as members with ILDs not known to be related to SSc in numbers higher than would be expected by chance, suggesting a shared genetic predisposition between SSc, SSc ILD and non SSc ILD. The heterogeneous nature of SSc complicates the interpretation of genetic studies and is a significant barrier to defining the genetic basis of SSc. Better characterization of phenotype may aid the understanding of scleroderma in general and the development of ILD specifically. Genomic studies is a recent advance that has begun to tease out specific signatures that correlate with different manifestations of SSc. For example, activation of genes controlled by TGFBetain are seen more often in patients with interstitial lung disease. This type of understanding will enhance studies of genetic factors related to SSc and will promote targeted therapeutic developments for different subtypes of scleroderma including those with ILD.

**Diagnosis of lung disease in scleroderma**

Respiratory symptoms in scleroderma lung disease can be quite nonspecific. At early stage, for instance, pulmonary fibrosis can advance without any symptoms. Dyspnea on exertion is the symptom usually first noticed which progresses until it presents at rest. The cough is often dry and non-productive. The tightness of chest is often reported, along with some nonspecific symptoms for instance the fatigue. Dyspnea could be due to ILD, some infrequent pulmonary manifestations, such as bronchiectasis, diffuse alveolar hemorrhage or its cause could be extra pulmonary like cardiac involvement, especially the left ventricular diastolic dysfunction, diminished thoracic cage expansions, neuromuscular, and pleural disease. It is rather challenging for the clinician to detect the underlying causes not only of breathlessness, but also other symptoms which can be due to different or even multiple causes, like fatigue. Fatigue may be seen in scleroderma lung disease, but also in active arthritis, myositis, fibromyalgia, or cardiac disease. Physical examination of the scleroderma patients is of utmost importance. It is to note that there is a minor group of patients with ILD, in which the ILD is

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the first, initial sign of scleroderma. The examination is usually rewarding as in most cases there are some signs that point to scleroderma if the search is thorough. The involvement of the lungs in scleroderma may be detected by auscultation, as in some patients the bibasilar late inspiratory fine crackles are identified. Examination findings of the pre-cordium may have a loud pulmonary component of second heart sound which is fixed or paradoxical split. If cor pulmonale develops, the signs are high-pitched systolic murmur of tricuspid regurgitation, hepatomegaly, a pulsatile liver, ascites, and peripheral edema.

**Pulmonary function testing**

Pulmonary Function Testing (PFTs) is an important component of the evaluation of dyspnea and in the detection of pulmonary involvement in patients with SSc. Patients with significant interstitial lung disease will demonstrate restriction on lung function testing although normal pulmonary function may be present in mild disease. Total Lung Capacity (TLC) by means of plethysmography is the most reliable measure of restriction and will confirm the presence of true lung restriction. However, spirometry which is more typically utilized in clinical practice provides a good estimation of true restriction. Spirometry provides measures of the Forced Vital Capacity (FVC) and the forced expiratory volume in one second (FEV1). In a restrictive lung disease, the FVC should be reduced and the FEV1/FVC ratio should be normal. It has been estimated that 40% patients with scleroderma have a FVC of less than 75% predicted, marking the presence of ILD. The diffusing capacity (DLCO) provides a measure of gas transfer between the air inhaled into the alveoli to the red blood cells in the systemic circulation. The DLCO is one of the most valuable measures in the evaluation of the scleroderma patients as a decreased value may be the earliest signal of lung disease in SSc and is reduced in 70% of SSc patients. Moreover, the DLCO correlates most closely with the degree of disease seen on the High Resolution Computed Tomography (HRCT) scan. The DLCO will be reduced in both pulmonary hypertension and ILD. Thus, the DLCO is not specific for the diagnosis of SSc ILD.

**Radiology**

The characteristic chest X-ray in scleroderma patients with ILD shows linear and reticular pattern, superimposed upon the ground-glass attenuation. Traction bronchiectasis may be detected, but contrary to the finding in Idiopathic Pulmonary Fibrosis (IPF), the honeycombing is rare. Evidence of pulmonary disease has been described in chest X-rays in 20–65% of patients affected by scleroderma. As with histology, the high resolution CT pattern in SSc-ILD is relatively homogeneous, again differing from other CTD-associated interstitial lung diseases, where a greater variety is present. In SSc-ILD, the most frequent CT pattern is either predominant ground-glass opacification or an admixed ground glass/reticulation pattern, with a predominant reticular pattern present in only one third of patients. In contrast, SSc-ILD and idiopathic Non-Specific Interstitial Pneumonia (NSIP) are less extensive, less coarse, and characterised by a greater proportion of ground glass opacification than IPF, supporting the biopsy series stating that NSIP is by far the commonest histological pattern in SSc-ILD. Ground glass on CT can represent either predominant inflammatory changes or fibrosis subliminal to the limits of resolution of HRCT. Although it is impossible to distinguish fibrosis from inflammation with certainty on the basis of HRCT, features suggestive of established fibrosis include admixed reticular abnormalities and the presence of traction bronchiectasis. However, even in the presence of these features, at least some of the ground glass may represent inflammatory changes, and the HRCT pattern can only be used as a rough guide in predicting possible reversibility with treatment.

**Bronchoalveolar Lavage (BAL)**

The role of BAL in patients with SSc ILD is controversial and in evolution. When a cell count is done on BAL from patients with SSc associated ILD, elevated numbers of granulocytes may be seen, especially neutrophils and eosinophils. Increased numbers of lymphocytes and mast cells may also be seen. Early studies correlated increased granulocytes in BAL with increased response to immunosuppression presumably because this represented active alveolitis. Subsequently, BAL granulocytosis has been shown to correlate with the degree of ground glass opacity seen on HRCT and with more advanced interstitial disease. However, data from the Scleroderma Lung Study suggest that BAL granulocytosis does not add any additional prognostic information to HRCT and pulmonary function measures and is not a predictor of treatment response.

**Biopsy**

Similar to radiographic appearances, there are a variety of histologic subtypes found in SSc ILD. In one series, NSIP was the more common histopathology occurring in 76% of the cases. In this same series, UIP occurred in 11% of the cases. There were also rare cases of organizing pneumonia and diffuse alveolar damage. Importantly, the clinical outcome does not correlate with the observed histology. Patients with scleroderma ILD can often experience stabilization after the initial development of their lung disease. In a series of 80 patients, survival does not differ between cellular NSIP, fibrotic NSIP and UIP. Thus, histology has no prognostic value. These patterns are in stark contrast to idiopathic ILDs where UIP is the most common pathology, the pathologic finding of UIP is associated with a poorer prognosis and stabilization of UIP for decades is rarely seen. Given this data, there is little value to a surgical biopsy in the evaluation of a
patient with scleroderma associated ILD. The exception to this may be in cases of an unusual CT pattern which does not fit a predicted pattern seen in SSc.

**Isotope lung scans:** To identify active lung inflammation in ILD or pulmonary emboli in PAH. Doppler echocardiography supplemented by electrocardiogram (ECG), are the traditional methods for investigating possible PAH, but their results can be misleading in scleroderma patients and definitive diagnosis requires direct measurement of Pulmonary Artery Pressure (PAP) by right heart catheterization. In ILD the echocardiogram is checked for pulmonary regurgitation and the pulmonary arterial systolic pressure is measured. If there is pulmonary regurgitation, the peak measurement is checked, and the size of the right ventricle is also checked to determine the amount of additional strain.

**Right heart catheterisation:** By passing a catheter through a vein into the heart, pressures in the heart chambers and major blood vessels leading from the heart to the lungs can be measured directly. Right heart catheterization remains the gold standard for diagnosis of PH. Apart the fact that PH is precisely estimated, the acute vasodilatation testing is also performed with inhaled nitric oxide, IV epoprostenol, or IV adenosine in order to determine the reversibility upon application of vasodilators, thus choosing the most appropriate treatment for a given patient. In patients with scleroderma, it is very important to rule out the existence of the left-sided heart disease, which is a frequent cause of PH in these patients. The right heart catheterization is the only method by which it can be ruled out.

### Monitoring and initiating treatment

Recommended investigations at baseline include PFT, chest X-ray, HRCT chest and echocardiogram. Serial monitoring of lung function tests, particularly in the first 5 years after diagnosis, is crucial for detection of onset and/or progression of SSc-ILD. HRCT chest can be omitted at baseline in ACA positive patients with normal PFTs, in view of the extremely low frequency of significant interstitial lung disease in this group. Immunosuppression should be considered in patients with severe and/or progressive disease. A cut-off of DLCO< 50% and/or FVC<70% together with significant extent of abnormalities on HRCT can be used to define severe disease and initiate treatment, unless there is documented stability on sequential PFTs over several years. Although not available in all centers, epithelial permeability markers such as DTPA clearance or serum KI-6, are powerful predictors of subsequent progression in SSc-ILD, and should be used in conjunction with other parameters.

![Algorithm for monitoring and initiating treatment for interstitial lung disease in patients with systemic sclerosis](image_url)
Therapies

Therapy for interstitial lung disease will not reverse scarring that has already taken place so it is important to diagnose and treat the condition as early as possible. The goals of treatment are to improve walking distance, dyspnea and quality of life. Unfortunately the rationalization of treatment has been hampered by a lack of enough double-blinded studies. The decision on who and when to treat is made by considering whether there is evidence of recent progression of the disease. Deterioration can be assessed by serial pulmonary function tests or chest radiography, duration and by autoantibody status. If there is a significant risk of disease progression and the risks associated with treatment (likely side-effects) are clearly outweighed by the risks associated with failure to treat (likely progression of disease) treatment should be introduced but it should be delayed if it is clear that disease is trivial and likely to remain stable. This judgment is sometimes very straightforward, but often the decision is a very close call and may require extra tests. Ideally, the patient should be introduced to these concepts and should then participate fully in decisions. Corticosteroids such as prednisolone or methylprednisolone may be given to reduce the inflammation. Due to concerns of an increased risk of scleroderma renal crisis high doses of corticosteroids are seldom used, although low doses (e.g. prednisone 10mg daily) continue to be prescribed, often in combination with immunosuppressive therapy. For some patients, steroids will help decrease inflammation and cause a dramatic improvement in symptoms while other patients may experience only partial improvement. Response to treatment depends on the amount of inflammation present and improvement may not be seen for up to 6-12 weeks. A chest X-ray, exercise tests and pulmonary function tests will determine whether a patient’s condition has been stabilized or improved. Cyclophosphamide may be used alone or in combination with steroids to reduce inflammation by killing some inflammatory cells and suppressing their function. These medications may take six months or longer to show improvement. Side effects include gastrointestinal irritation, bladder inflammation, bone marrow suppression, infection, irregular menstruation and blood disorders. The Scleroderma Lung Study evaluated 162 patients randomized to receive either placebo or oral cyclophosphamide (in addition to low dose prednisolone) for one year41. The study met the primary outcome, the observed absolute difference in FVC% at 12 months between treated and untreated patients, although the difference was small. Interestingly, the largest effect was seen in patients with more severe lung fibrosis, as assessed by CT scoring, emphasizing the importance of patient selection41. Among secondary outcome measures, a significant, but again small, beneficial effect was observed in the skin thickness and dyspnea scores. Oral versus intravenous cyclophosphamide as evidenced by oral cyclophosphamide Scleroderma Lung Study have the same magnitude in terms of outcome. The difference is IV cyclophosphamide is less toxic (hematuria, haemocytopenia) than oral cyclophosphamide. Furthermore, although long term follow up data was lacking, experience gained in the treatment of other autoimmune disorders, indicates that intermittent monthly iv boluses of cyclophosphamide are associated with lower risks of cancer and gonadal failure compared to oral daily administration of the drug42. Unresolved issues regarding treatment include which long-term immunosuppressive agents to use after the induction period with cyclophosphamide, so as to minimize cyclophosphamide-induced morbidities. The immunosuppressant azathioprine can be used as maintenance following induction with cyclophosphamide as shown in the FAST trial. The FAST trial (fibrosing alveolitis in scleroderma trial) performed in 45 patients, comparing placebo with monthly intravenous cyclophosphamide for 6 months, followed by oral azathioprine and low dose prednisone for a total of 24 months43. Although this study did not reach a significant result, there was a clear trend towards a difference in change in FVC at one year in the treatment group (p=0.08), with a 4.19% change in FVC at one year favouring the treatment group. The similar results obtained in the FAST trial in which six months of cyclophosphamide were followed by azathioprine, suggest that a protocol of induction (with cyclo) / maintenance (with less toxic immunosuppressants) regimen is a viable option. Though it has been proven inferior in efficacy to corticosteroids and/or cyclophosphamide, azathioprine can be given to patients who have problems tolerating the side effects of corticosteroids and/or cyclophosphamide as first line treatment protocol. Side effects of azathioprine may include fever, skin rash, gastrointestinal irritation and blood disorders. Other immunosuppressants, such as cyclosporine and tacrolimus may also be used. However, cyclosporine can cause renal impairment while tacrolimus can cause type 2 diabetes. Both colchicine and D-penicillamine are occasionally prescribed. Both agents have the advantage that major toxicity is rare. However, there is a complete lack of compelling circumstantial evidence that either treatment is effective in lung disease. Their use can therefore be seriously questioned, especially if it results in delays in starting more effective treatment. A group of medications currently being developed are the antifibrotic agents which act directly to limit scar tissue formation. These agents are not available routinely but are being investigated around the world in clinical trials. The endothelin receptor antagonist bosentan (Tracleer) has already been shown to be effective in patients with scleroderma and PAH. It is being studied in patients with ILD associated with scleroderma as well as patients with idiopathic pulmonary fibrosis. Endothelin (ET-1) is a key mediator of disease processes in PAH levels of ET-1 are elevated in PAH and can cause vasoconstriction, inflammation, fibrosis and vascular hypertrophy. This is through binding to two receptor subtypes, ETA and ETB. Novel therapies include ETA antagonist sitaxsentan, which is currently being investigated in PAH and has...
shown positive results as it significantly improved exercise capacity and cardiopulmonary haemodynamics during a 12-week trial in a group of PAH patients including those with connective tissue disease. Final data are still to be established on the use of this compound in PAH\(^4\). Ambisentan, another ETA antagonist, is being evaluated and preliminary results show improvements in exercise capacity and haemodynamics. There are randomized clinical trials currently ongoing on ambisentan to further explore its efficacy and side effects\(^1\). Novel immunomodulatory treatments (such as the tumour necrosis factor inhibitors infliximab (Remicade) and etanercept (Enbrel)) are being studied in patients with idiopathic pulmonary fibrosis. The disease modifying anti-rheumatic drug methotrexate may also be used. Studies are also ongoing with an anti-CTGF (connective tissue growth factor) antibody and with subcutaneous recombinant interferon-g1b in patients with idiopathic pulmonary fibrosis. Oxygen therapy may help reduce shortness of breath and prevent other complications and may allow those affected by ILD to feel better and lead a more active life.

Rituximab is a chimeric monoclonal antibody against human CD20 that depletes peripheral B cells. It has been introduced with some success in the treatment of systemic rheumatic diseases and exhibits an acceptable safety profile. In the pathogenesis of scleroderma evidence suggests B cells may be actively involved in the fibrotic process\(^2\). B cells are over activated in both experimental models of fibrosis as well as in humans with SSc. Rituximab has been tried in SSc with promising results\(^3\). In a randomized controlled study it was shown that treatment with two courses of rituximab leads to a significant improvement of lung function at one year compared to baseline\(^4\). The study was not able to exactly say how rituximab mediates its beneficial effects in SSc. However, rituximab seems to have a broad effect on the immune system, beyond B cell depletion, and therefore other mechanisms may apply e.g. significant decrease in Platelet Derived Growth Factor (PDGF) receptor expression and activation in the skin\(^5\). They also noted it had a better safety profile. Recently, the Rituximab group of EUSTAR reported encouraging results in 72 patients with SSc treated with rituximab\(^6\). We still need more randomized studies with larger numbers of participants. If rituximab turns out to be effective, it would be a major therapeutic advance in SSc since it can be administered on a long term basis due to its acceptable safety profile.

Lung transplantation may offer hope for some people with severe ILD. Until recently, very little data was available on the outcome of lung transplantation in scleroderma, with only a handful of cases found in the published literature\(^7\). Schachna et al\(^8\) in a study compared long term survival in 29 patients with scleroderma, 70 with IPF and 38 with idiopathic pulmonary hypertension, representing the total number of transplants for these conditions in two US centers over a 12 and half year period following lung transplants. Indications for transplantation amongst those with scleroderma were interstitial lung disease in 15 patients, pulmonary arterial hypertension in 11 and both in three patients. Despite the common perception that systemic disorders may be a contraindication to transplant, the study concluded that scleroderma patients undergoing lung transplantation have similar rates of survival to the two other lung-only disorders at two years, although there was a nonsignificant trend towards a higher early mortality within the first six months. There is need for more research on transplantation in scleroderma.

**Future directions**

In view of the toxicities of the current immunosuppressive regimens and poor outcomes of patients despite being on optimal current management, alternative, more effective treatment options are needed. The activation of T and B cells early in the course of the disease suggests that these cells and their cytokines are potential targets for therapeutic interventions\(^9\). Approaches that alter the balance between TH1 and TH2 cytokines by inhibiting TH2 cytokines, have been shown to be beneficial in animal models of SSc\(^10\). Another potential source of hope would be pro-fibrotic cytokines, TGFβ and CTGF. These are natural treatment targets, and have been evaluated in a Phase I/II trials to assess safety and tolerability though the results have been largely disappointing\(^11\). Despite the recent advances in therapies still the prognosis of pulmonary manifestations of scleroderma is poor. Further understanding of the molecular mechanisms through which vascular disease, autoimmunity and fibrosis interlink will inevitably lead to improved treatment strategies in SSc.

**Conclusion**

Pulmonary complications are common in SSc and are the leading causes of death. Careful evaluation by the clinician is warranted to detect the presence of an ILD and to select patients appropriately for consideration of therapy. Exertional dyspnea and dry cough are the most common presenting symptoms in patients with SSc who develop pulmonary involvement. Early initiation of therapy should be particularly considered in patients with early disease, clinical progression and evidence of alveolitis. Unfortunately, systemic sclerosis lung disease is often not detected or diagnosed until the late stages, particularly in those who did not develop the classic signs of skin-hardening or sclerodactyly, or those who only exhibited subtle respiratory symptoms. At the current time, cyclophosphamide remains the best studied therapeutic agent although alternatives are actively being evaluated. The pathogenesis of SSc-ILD is still an enigma and is being actively researched. This will advance our understanding of the disease and ability to care for these patients. Clinical trials are underway and
offer hope for novel approaches to this mysterious and often devastating manifestation of scleroderma.

References


Clinical pattern of knee osteoarthritis in patients seen at rheumatology clinic of Aminu Kano Teaching Hospital, Northwestern Nigeria

Ibrahim DA¹, Borodo MM¹, Adelowo OO²

Abstract

Background: Although osteoarthritis is a frequent and important cause of pain and disability worldwide, its pattern of joint involvement varies from place to place.

Objective: To determine the clinical pattern of knee osteoarthritis in patients seen at the rheumatology clinic of Aminu Kano Teaching Hospital.

Design: A prospective, cross sectional, descriptive, hospital-based study was carried out, from the 1st June to 30th November 2009.

Methods: Adults aged 18 years and above referred with knee pain were evaluated.

Results: One hundred and seventy four osteoarthritic knee involvements in 100 patients were evaluated. There were 27 males and 73 females, giving a F:M ratio of 2.7:1, with mean age of 56.92 ± 12.71 years. The mean BMI of the patients was 29.68 ± 4.87 Kg/M² and 18% reported previous trauma to the knee. Eleven per cent of the patients had features of benign joint hypermobility syndrome. The median duration of knee pain before presentation was 30 months (range 3-180). Forty per cent of the patients had history of knee swelling, with a median duration of 24 months (range 1-120) before presentation. Majority of the patients (92%) had morning stiffness, with a median duration of 10 minutes (range 0-60).

There was knee tenderness (in all patients), knee swelling (44%), knee crepitus (95%), knee deformities (34%), decreased range of motion (64%) and decreased quadriceps strength (82%) were observed. Majority of the patients’ radiographs showed KL grade 3 (44%) or 4 (38%) features. The Medial Tibio-Femoral (MTF) compartment was affected in 92% of the patients while the Lateral Tibio-Femoral (LTF) compartment was affected in 66% and the Patella-Femoral (PF) compartment in 80% of the patients. Associated hand OA was noted in 13% of the patients, while OA affecting other sites were observed in 32%. Majority of the patients were in functional class I or II.

Conclusion: The clinical pattern seen in our patients is similar to what was reported elsewhere in Africa and contrasts with reports in caucasians where associated generalized osteoarthritis and hip joint disease are more common.

Keywords: Clinical, Pattern, Knee, Osteoarthritis

Introduction

Osteoarthritis (OA) can be defined by either joint symptoms, or structural pathology (e.g. on X-ray), or by the combination of the two. The primary symptoms include joint pain, stiffness, and difficulty in walking. The joint pathology is diverse and includes focal damage and loss of articular cartilage, abnormal remodeling and attrition of subchondral bone, osteophytes, ligamentous laxity, weakening of periarticular muscles, and in some cases synovial distention and inflammation¹. All tissues of the joint are involved, although the loss of articular cartilage and changes in adjacent bone remain the most striking features¹. In this regard, OA represents failure of the joint as an organ,
analogous to renal or cardiac failure, and the pathological observations in advanced disease are as much a product of attempted repair as of the primary insult or damage which contributed to the initiation of the process\textsuperscript{1}. The knee joint is the commonest site affected by OA in Nigerians\textsuperscript{2-5} as is the case globally\textsuperscript{1}.

As a result of its effect on ambulation and mobility, OA of the knee has significant functional impact and is associated with considerable medical costs from surgeries, accounting for most of the 478,000 total knee replacements for arthritis in 2004 in United States (US)\textsuperscript{6}.

Although adequate information exists on the pattern of the disease in the developed countries,\textsuperscript{7,8} there are few studies from tropical West Africa\textsuperscript{2-5}. Apart from the above mentioned studies in another part of Nigeria, we were unable to find any previous reports on how the pattern of osteoarthritis of the knee in this region (Northwestern Nigeria) compared with the pattern of the disease elsewhere.

Materials and Methods

This was a prospective, cross-sectional, descriptive, hospital-based study carried on adults aged 18 years and above, referred with clinical and radiographic evidence of knee OA (as defined by the ACR Criteria)\textsuperscript{9} to the Rheumatology Clinic of AKTH, Kano. A pre-tested questionnaire was administered to each patient after obtaining an informed consent, and relevant information on biodata, history of the knee OA, anthropometry as well as clinical and radiographic evaluation of the knees were performed. Standard radiographs as suggested by Ahlback\textsuperscript{10} were done (i.e. standing semi-flexed and skyline views) where necessary. Kellgren and Lawrence Criteria\textsuperscript{11} were used to grade the findings. Other symptomatic joints were also evaluated and recorded.

Data obtained were analysed using the Statistical Package for Social Sciences (SPSS) version 16.0 and a p-value of < 0.05 was considered significant. The study was conducted from the 1\textsuperscript{st} June, 2009 to the 30\textsuperscript{th} November, 2009.

Results

One hundred and seventy four osteoarthritic knees from 100 patients were evaluated. There were 27 males and 73 females, giving a F:M ratio of 2.7:1. The mean age of the patients at presentation was 56.92 ± 12.71 years. The peak age group was 60-69 years (29%), with up to 29% of the patients below 50 years. Table 1 depicts the patient’s characteristics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Males</th>
<th>Females</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
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<td>73</td>
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</tr>
<tr>
<td>Age groups (years)</td>
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</tr>
<tr>
<td>10-19</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20-29</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>30-39</td>
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<td>5</td>
<td>10</td>
</tr>
<tr>
<td>40-49</td>
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</tr>
<tr>
<td>50-59</td>
<td>8</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>60-69</td>
<td>7</td>
<td>22</td>
<td>29</td>
</tr>
<tr>
<td>70-79</td>
<td>5</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>≥80</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ethnicity</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hausa</td>
<td>16</td>
<td>49</td>
<td>65</td>
</tr>
<tr>
<td>Fulani</td>
<td>3</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Kanuri</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Yoruba</td>
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<td>4</td>
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</tr>
<tr>
<td>Igbo</td>
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</tr>
<tr>
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<td>3</td>
<td>4</td>
</tr>
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<td></td>
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</tr>
<tr>
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<td>19</td>
<td>24</td>
</tr>
<tr>
<td>Skilled/Professional</td>
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<td>18</td>
<td>24</td>
</tr>
<tr>
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<td>15</td>
<td>17</td>
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<tr>
<td>Unskilled labour</td>
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<td>7</td>
</tr>
<tr>
<td>Domestic servants</td>
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<td>5</td>
<td>6</td>
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<td>0</td>
<td>3</td>
</tr>
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<td>Others</td>
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<td>15</td>
<td>19</td>
</tr>
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<td>Educational status</td>
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<td></td>
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</tr>
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<td>4</td>
<td>17</td>
<td>21</td>
</tr>
<tr>
<td>Primary graduates</td>
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<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Qur’anic education</td>
<td>10</td>
<td>23</td>
<td>33</td>
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</tbody>
</table>

All (100%) patients reported with knee pain. Seventy eight (78%) had pain in both knees, 12 (12%) had pain in only the left knee while 10 (10%) had pain in only the right knee. The median duration of knee pain before presentation was 30 months (range 3-180). Forty (40%) patients reported history of knee swellings. Both knees were reported swollen in 18 (18%) patients. Eleven (11%) patients each reported swelling of either left or right knee alone. The median duration of knee swelling before presentation was 24 months (range 1-120). There were 92 (92%) patients that reported history of early morning and/or after rest stiffness in their knees. The median duration of stiffness was 10 minutes (range 0-60). Sixty four (64%) of the patients reported having difficulty going up and/or down the stairs. Eighteen (18%) patients had history of trauma to the knee (mostly home accident), 13 (13%) of which were females while 5 (5%) were males. There was no significant statistical difference between the sexes, p = 0.935.

Only 7 (7%) patients had previous medical and/or surgical procedure on the knee(s). Five patients had foreign body removed (mostly sewing needle), while the remaining two were closed arthrocentesis, all in known
sickle cell anaemia patients. Thirty six (36%) patients were using a walking aid at presentation; and the walking stick was used in 35 patients, while 1 patient was using a walking frame. Paracetamol was used by 57 (57%) patients, while 22 (22%) used various NSAID’s and 9 (9%) had steroids injected into their knees. Twelve (12%) patients had used various traditional medications, which included bloodletting and herbal remedies.

The mean weight of the patients was 79.48kg ± 11.74. The mean weight for males was 79.07kg ± 11.95 while for females was 79.62kg ± 11.74. The patients had a mean height of 1.64meters ± 0.066. The mean height for males was 1.69meters ± 0.0462 while for females was 1.62meters ± 0.0608. The mean BMI of the patients was 29.68kg/m² ± 4.87. The males had a mean BMI of 27.55kg/m² ± 3.95 while the females had a mean BMI of 30.47kg/m² ± 4.96. Forty one (41%) of the patients were obese.

Knee tenderness was elicited in all (100%) patients, either along the medial and/or lateral knee joint lines or the patella. Eighty (80%) patients had tenderness of both knees, 12 (12%) were only tender on the left knee while 8 (8%) were only tender on the right knee. Knee swelling was demonstrated in 44 (44%) patients. Swelling was either bony, fluid, soft tissue or a combination. Of these 44 patients, 24 had both knees swollen, 13 had swollen left knee only while 7 had swollen right knee only. Table 2 shows the other knee clinical examination findings. Majority of the patients’ radiographs showed KL grade 3 (44%) or 4 (38%) features. The medial Tibio-Femoral (MTF) compartment was affected in 92% of the patients while the Lateral Tibio-Femoral (LTF) compartment was affected in 66% and the Patella-Femoral (PF) compartment in 80% of the patients.

Among the study group, 13 (13%) patients were found to have evidence of hand osteoarthritis, mainly affecting the 2nd and 3rd DIP’s. Ten were females while three were males. Thirty two (32%) patients showed clinical and/or radiographic evidence of osteoarthritis in other joints (excluding hand OA). Twenty six (26%) were females, with 6 (6%) males, (p = 0.202). Symptomatic Lumbar Spondylosis was present in 27 patients, hips were affected in 6 patients, shoulders in 4 patients, while the ankles in 11 patients. The 1st metatarsophalangeal joints were affected in 17 patients. Eleven (11%) patients showed evidence of Benign Joint Hypermobility Syndrome (BJHS) 2, 4, 5, 7 were females and 4 males, (p = 0.458). Majority of the patients were either in class I (45%) or class II (47%) functional disability state (as assessed using the Steinbrocker’s Criteria) 3, with 8 (8%) patients in class III. None of the patients was in class IV, (p = 0.243).

### Table 2: Knee examination findings in the patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Males</th>
<th>Females</th>
<th>Total (%)</th>
<th>P value</th>
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<tbody>
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<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Left</td>
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<td>7</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>6</td>
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<td></td>
</tr>
<tr>
<td>Both</td>
<td>10</td>
<td>47</td>
<td>57</td>
<td></td>
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<tr>
<td>Knee deformity</td>
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<td></td>
<td></td>
<td>0.013</td>
</tr>
<tr>
<td>(Varus)</td>
<td>22</td>
<td>57</td>
<td>79</td>
<td></td>
</tr>
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<td>10</td>
<td>12</td>
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<tr>
<td>Both</td>
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<td></td>
<td></td>
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<tr>
<td>Knee deformity</td>
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<td>0.013</td>
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<tr>
<td>(Valgus)</td>
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<tr>
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<tr>
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<td>64</td>
<td></td>
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<tr>
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<tr>
<td>Decreased</td>
<td>20</td>
<td>62</td>
<td>82</td>
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</table>

### Discussion

The preponderance of women with knee OA observed in this study is similar to observations earlier made in Ibadan, 2, 4, 5 South African blacks 13 and in studies of the white populations 1. However; the female preponderance was less marked in our study, perhaps because some of our patients were relatively young, with features of Benign Hypermobility Syndrome. It is known that the female to male ratio in this disease increases with age 14. The slightly earlier age of onset of the disease in our patients compares with what others from Nigeria found 2, 4, 5. Twenty-nine per cent of the patients were 50 years and below, which may reflect the younger mean age of our study population when compared with subjects in Caucasian populations. The reason for this younger age of onset in our patients is unknown, and no obvious predisposing cause was found in most cases. A study by Ebong 2 suggested that the onset of symptoms in the disease at an early age was unfavourable with regard to the development of pain.

Although patients of all categories of educational background were seen in this study, however, more University/Diploma graduates attended our clinic which may be a result of more health awareness in them rather than a reflection of their social status.

Paracetamol, domestic work and professional/skilled work as well as teaching were the predominant occupations for females in this study, while most men...
were unskilled labourers or subsistent farmers. Adelowo3 has suggested association between knee OA and women traders who sit on low stools, about a foot off the ground with their knees in extreme flexion. This position may subject their knee joints to minor trauma and uneven wear. The same observation was made by Adebajo5. Our study also supported these observations. Apart from kneeling for prayers; women are required to kneel as a form of greeting to their elders.

Trauma was apparently a less significant factor in OA of the knee in Kano patients, as in Ibadan2,4,5 than in Caucasians. In Caucasian males, trauma was found to be associated with OA of the knee in about half of the cases4. This is not apparent in this study, especially with poor recall of previous history of trauma as a possibility in our patients. It may also be that differences in occupational hazards partly accounted for this difference. For instance, most of the men in the Caucasian study by Kellgren and Lawrence6 were coal miners, in whom knee injury was quite common.

The role of obesity in causation of knee OA has long been established15. It preceded its development by many years16-18 and hastens the structural worsening of existing knee OA19,20. About three-quarter of the patients in our study were either overweight (37%) or obese (41%). In another series from Ibadan2, however, only a quarter of the females were overweight.

Hypermobility was seen in more than 10% of the patients, most of whom manifested this feature at a relatively young age. In a personal communication, Adelowo made a similar observation, though Adebajo5 observed much less figures. Repeated minor trauma to the ligaments and tendons around the knee in patients with hyper mobile joints may explain the early onset of degenerative changes.

Assessment of the causal relationship of quadriceps weakness and knee OA is problematic in case of asymptomatic knee OA, as is the case in our study. Most of the patients had decreased quadriceps strength, which was bilateral in two-thirds. Knees with existing OA are known to have weaker quadriceps than knees without OA, especially when symptoms are present (probably due to disuse atrophy). But weakness is also present in knees without pain or evidence of muscle atrophy, possibly due to arthrogenous inhibition of muscle contraction21.

About a third of the patient’s knees were found to have either varus and/or valgus deformities, and the deformities were bilateral in about a fifth. Knee deformities are very common in Nigerian children2, and some adults are seen with neglected gross deformities starting from childhood. It is not possible to say categorically from our study whether the observed deformities were the cause or result of knee degeneration. We found more valgus deformity than varus, and this was even more so in women than in men (p= 0.013). Ebong2 made a similar observation in Ibadan, with 22 knees having valgus compared to three knees with varus deformity. OA knees with a varus or valgus malalignment have 3-4 fold increased risk of further joint space narrowing in the medial or lateral compartment respectively22.

Pain, the cardinal symptom of symptomatic knee OA, was present in all the cases, as it was in Ibadan patients2. By definition, symptomatic OA patients will have pain at involved sites, in addition to other clinical and radiological features. Majority (92%) of our patients also had stiffness, while only half of Ibadan patients had stiffness. However, history of knee swelling was similar to Ibadan patients2 in our study.

Majority of the patients’ knees were tender (180 of the 200 knees), signifying bilateral affection of the knees with the disease. It is known that with the passage of time, unilateral knee OA tends to progress to bilateral knee OA due to excessive loading of the initially unaffected knee23. A third (34%) of the patients’ knees were swollen, either with fluid or by bony osteophytic outgrowths. None of our patients had Baker’s cyst or ruptured popliteal cyst. It is known that herniation or rupture of a bursa into the thigh or leg (herniated or ruptured popliteal cyst) may complicate knee OA, simulating thrombophlebitis (pseudothrombophlebitis syndrome)24.

Crepitus of the knee is one of the ACR diagnostic criteria6 for knee OA. This was present in (152) 76% knees of our study group. Its presence, especially on active movement, may limit patient’s function and decrease quality of life.

With the progression of knee OA, the range of motion of the affected knee tends to decrease, subsequently leading to fixed flexion deformities with/without bony ankylosis. Majority of the patients in this study had some evidence of abnormal knee range of motion, signifying advanced stage of the disease at presentation. However, some of our patients presented relatively early (mean duration of symptoms before presentation was 43.21±36.93 months), which compares with Caucasian studies. It may imply that their disease is rapidly progressing. This observation requires further evaluation in a study specifically designed to address rate of disease progression from onset. The radiographic appearances in our patients were similar with the recognized pattern2,4,5,13,25.

The paucity of Heberden’s nodes in our study was striking, as well as metacarpophalangeal and carpometacarpophalangeal joints disease, in support of the view that such disease is usually linked to generalized OA. Adebajo5 made similar observations. However, reports from Burkina Faso26 reported a high prevalence of Heberden’s nodes in their knee OA patients.

The hip joints, commonly involved in Caucasians, were affected in only six patients. A similar low frequency was reported in Nigeria2,4,5 and among the Chinese25. The Nigerian ethnic groups assumes a squatting position most especially during defaecation and other religious and daily activities. This was postulated to be protective against the development of hip OA25.

Polyarticular osteoarthritis affecting three or more joint sites was uncommon in our patients, and occurred in only six patients. In contrast, the incidence of multiple osteoarthritis in an English series was 24%. The reason for this lower incidence of polyarticular OA in African
Black is not known, but this observation has been reported previously.\(^2\)\(^3\)

Osteoarthritis, especially of the weight bearing joints, is known to affect functional status. This depends on the severity and associated co-morbid conditions of the patients. Majority of the patients in our study were either in functional class I or II. A few (8%) were in functional class III.

**Conclusion**

The clinical pattern of knee OA seen in our patients is similar to what was reported elsewhere in Africa and contrasts with reports in caucasians where associated polyarticular (generalize) osteoarthritis and hip joint disease are more common.

**References**

An evaluation of quality of life in ambulatory patients with systemic lupus erythematosus attending rheumatology clinic in Kenyatta National Hospital

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Abstract

Background: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that affects all organs of the body. It is becoming increasingly clear that SLE is not as rare in Kenya as was previously thought. Due to its chronicity SLE has been known to affect the quality of life of those affected by it. There is minimal data on SLE in East Africa and especially in Kenya. The quality of life of SLE patients in this country has never been assessed.

Objectives: To document the quality of life of patients with SLE in Kenyatta National Hospital using LUPUS QOL questionnaire. We also sought to correlate HRQOL with duration of illness, drugs used and age of the patient.

Design: This was a cross sectional study done on patients attending Rheumatology clinic in Kenyatta National Hospital.

Methods: Patients who satisfy the ACR criteria were consecutively recruited. All patients with SLE attending the clinic were included in the study. Consent was obtained from the patients after which their demographic data was obtained. Patients were examined for the presence of malar rash, discoid rash, arthritis/athralgia, photosensitivity, CNS symptoms, serositis and oral ulcers. The patients then filled the LUPUS QOL questionnaire. The information acquired was then analysed using SPSS version 17.0 using student t test and regression analysis. The quality of life was calculated and then correlated with age, duration of illness and drug management.

Results: Sixty two patients were analysed (60 females 2 males). Mean age of the population was 37.3 years (range 14-71 years). All patients had some level of education with 61.3% of the population having some form of secondary education. Most patients 54.8% were married. Mean age of diagnosis was 34.5 years with mean duration of illness 1.5 years. Majority (88.7%) had arthritis/arthralgia, oral ulcers (62.9%), malar rash (59.7%), photosensitivity (58.1%), serositis (32.3%), CNS symptoms (27.4%) discoid rash (17.7%). Patients scored globally low in all domains of LUPUS QOL. Highest domain was planning 63.7 (29.3), emotional health 61.3 (26.5), burden to others 58.9 (31.2), fatigue 57.5 (30.0), pain 56.6 (29.6), physical health 54.0 (23.3), body image 47.1 (24.2) intimate relations 41.1 (38.4).

The most common drug in use in our population was prednisone at 74.2%. This was followed by HCQ at 69.4%, NSAIDS 54.8%, azathioprine 37.1%, methotrexate 22.6%, mycofenolate mofetil 8.1%, CCB 11.3%, cyclosporine 3.2%. HRQOL correlated positively with advance in age for the domains. Physical health, burden to others, emotional health and fatigue. There was no correlation between HRQOL and duration of illness or drugs used by the population.

Conclusion: The HRQOL of our SLE patients was found to be low in all domains and to correlate with advance in age in the domains of physical health, burden to others, emotional health and fatigue. However there was no correlation with duration of illness or the drugs used by the patients.

Introduction

According to WHO, health is defined as the individual’s perception about his/her physical, mental, and social well being, and not merely the absence of disease or infirmity1. It comprises of several domains i.e. physical health, psychological status, degree of independence, social relationship, beliefs, relationship with the environment, financial gain, and freedom. Measured of QOL consider the effects of the disease or its treatment from the patient’s perspective and determine the need for social, emotional and physical support during illness.

Systemic lupus erythematosus is characterized by periods of active disease
and remission with better healthcare. The survival of SLE patients has significantly improved over the past years. It is now becoming clear that disease status in chronic conditions is not only measured by the physical condition of the patient but also psychosocial factors such as pain, apprehension, difficulty in fulfilling personal and family responsibilities, financial burden and diminished cognition. Assessing the Quality of Life (QOL) is thus an important measure to assess how much the disease process and its treatment is affecting an individual. Khanna et al. found that higher disease severity was associated with a lower quality of life score especially in the physical and psychological aspects but no significant correlation with social and environmental domains in the QOL. Patients with clearly active and probably active disease had significantly lower scores in the physical and psychological domains than patients with inactive disease. However, no significant difference was found in the domains of social and environmental QOL. Age or disease duration did not affect the QOL in any of the domains.

LUPUS QOL was developed to measure disease specific Health-Related Quality of Life (HRQOL) in adults with Systemic Lupus Erythematosus (SLE). It was developed and validated in the UK by McElhone et al. in 2007. It has 8 individual subscales physical health (8 items), emotional health (6 items), body image (5 items), pain (3 items), planning (3 items), fatigue (4 items), intimate relationships (2 items), burden to others (3 items). The Questionnaire has a 5-point Likert scale response format (0 all the time, 1 most of the time, 2 a good bit of the time, 3 occasionally, and 4 never). It has a recall period of the prior 4 weeks. It is available in both written and electronic versions. Scores range from 0 (worst HRQOL) to 100 (best HRQOL). The score ranges from 0 (worst HRQOL) to 100 (best HRQOL).

Materials and Methods

Patients diagnosed with SLE as by the ACR criteria and confirmed by a rheumatologist and gave informed consent (assent for minors), were recruited into the study. Those who declined to participate in the study were excluded. The patient’s demographic data and last prescription was acquired from the file. The patients were then taken through some counseling to ascertain what they knew about their disease and to clear any misconceptions they may have had concerning their illness and treatment. Patients’ clinical history was taken and a physical exam was then done. An observation was made for the presence of malar rash, discoid rash, arthritis/arthralgia, serositis, photosensitivity. These were defined as per the ACR criteria. After this the patient was given the LUPUS QOL questionnaire to fill. All the patients who attended the clinic were included in the study.

Data management and statistical analysis: Data was collected using structured questionnaires and was cleaned for errors and conflicting answers, missing entries and duplicate entries. The cleaned data was then exported to SPSS version 17.0 for analysis. Demographic variables (age) were summarized into means/ medians while gender, marital status were presented using percentages. Correlation of HRQOL and age, duration of illness and medication used was done using regression analysis.

Results

Demographic characteristics: Sixty seven patients were screened according to patients’ records. The patients were then contacted by telephone and asked to participate in the study. Three had passed away, two declined to participate. Therefore 62 patients were recruited into the study. Table 1 shows the baseline characteristics of our population.

Table 1: Baseline characteristics of our population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>37.3 (12.2)</td>
</tr>
<tr>
<td>Min-Max</td>
<td>14-71</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>60 (96.8)</td>
</tr>
<tr>
<td>Male</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>8 (12.9)</td>
</tr>
<tr>
<td>Secondary</td>
<td>16 (25.8)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>38 (61.3)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>26 (41.9)</td>
</tr>
<tr>
<td>Married</td>
<td>34 (54.8)</td>
</tr>
<tr>
<td>Divorced</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Age at diagnosis, mean (SD)</td>
<td>34.5 (12.2)</td>
</tr>
<tr>
<td>Duration of illness in years, median (IQR)</td>
<td>1.5 (0.08-12) (0.8-3.0)</td>
</tr>
</tbody>
</table>

Distribution of common lupus clinical features in our population: Majority of the patients (88.7%) had arthritis or arthralgia. This was followed by oral ulcers at 32.3%, malar rash 59.7%, photosensitivity 58.1%, serositis 32.2%, CNS 27.4%. The least common clinical feature was discoid rash 17.7%. Figure 1 shows the distribution of the clinical features in the population.

Figure 1: Distribution of clinical features of lupus in the population
Health Related Quality of Life: On assessment of the HRQoL, Our population scored globally low in all the domains. The domain with the highest scores was planning (63.7), followed by burden to others (58.9), fatigue (57.5), pain (56.6), physical health (54.0), body image (47.1) and the lowest intimate relationships (41.1) as elaborated in Table 2.

Table 2: LUPUS QOL scores of our population

<table>
<thead>
<tr>
<th>Domain</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical health</td>
<td>54.0 (23.3)</td>
</tr>
<tr>
<td>Pain</td>
<td>56.6 (29.6)</td>
</tr>
<tr>
<td>Planning</td>
<td>63.7 (29.3)</td>
</tr>
<tr>
<td>Intimate relations</td>
<td>41.1 (38.4)</td>
</tr>
<tr>
<td>Burden to others</td>
<td>58.9 (31.2)</td>
</tr>
<tr>
<td>Emotional health</td>
<td>61.3 (26.5)</td>
</tr>
<tr>
<td>Body image</td>
<td>47.1 (24.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>57.5 (30.0)</td>
</tr>
</tbody>
</table>

Current drug management in our population: The patients’ last prescription was recorded. Most common drug in use by our population was prednisone at 46(74.2%). This was followed by hydroxychloroquine (HCQ) at 43(69.4%). NSAIDS were the third most prescribed drug with 34 patients (54.8%). Twenty three patients were on azathioprine (37.1%). Methotrexate (MTX) was used by 14 (22.6%). The other drugs used by the patients were; Mycofenolate Mofetil (MMF) 5(8.1%) CCB 7 (11.3%), cyclosporine 2(3.2%). Of note is that the seven who were using CCB were all using it at antihypertensive doses. No one was using it for Reynaud’s phenomenon. Figure 2 shows this distribution.

Figure 2: Distribution of drug use in the population

Correlation of HRQOL with age: Quality of life scores of the population was correlated with age for each domain. Positive correlation was found between physical health (r 0.306 p value 0.016), burden to others (r=0.272 p= 0.032) and emotional health (r=0.315, p= 0.013) and advance in age.

Correlation of HRQOL score and duration of illness: There was no significant association between HRQOL and the duration of illness, as shown in Table 4.

Table 3: Correlation of HRQOL score and age in our population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pearson coefficient (r)</th>
<th>β (95% CI of β)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical health</td>
<td>0.306</td>
<td>0.58 (0.11-1.05)</td>
<td>0.016</td>
</tr>
<tr>
<td>Pain</td>
<td>0.128</td>
<td>0.31 (-0.31-0.93)</td>
<td>0.321</td>
</tr>
<tr>
<td>Planning</td>
<td>0.197</td>
<td>0.47 (-0.14-1.08)</td>
<td>0.125</td>
</tr>
<tr>
<td>Int. Relation</td>
<td>0.025</td>
<td>0.08 (-0.74-0.90)</td>
<td>0.848</td>
</tr>
<tr>
<td>Burden to others</td>
<td>0.272</td>
<td>0.72 (0.06-1.39)</td>
<td>0.032</td>
</tr>
<tr>
<td>Emotional heath</td>
<td>0.315</td>
<td>0.682 (0.15-1.21)</td>
<td>0.013</td>
</tr>
<tr>
<td>Body image</td>
<td>0.147</td>
<td>0.29 (-0.22-0.80)</td>
<td>0.258</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.268</td>
<td>0.58 (0.03-1.14)</td>
<td>0.039</td>
</tr>
</tbody>
</table>

Association between QOL and drugs used: The study looked for any association between HRQOL and medication used in our population and also looked at the three most common drugs used i.e. prednisone, HCQ and NSAIDS. Again we found no significant correlation with the drugs used. Table 5 shows our findings.

Table 5: Association between HRQOL and prednisone

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prednisone</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical health</td>
<td>Yes (n=46)</td>
<td>53.1 (23.1)</td>
</tr>
<tr>
<td>Pain</td>
<td>No (n=16)</td>
<td>55.1 (29.5)</td>
</tr>
<tr>
<td>Planning</td>
<td>Yes (n=46)</td>
<td>61.4 (28.6)</td>
</tr>
<tr>
<td>Int. Relation</td>
<td>No (n=16)</td>
<td>39.8 (37.9)</td>
</tr>
<tr>
<td>Burden to others</td>
<td>Yes (n=46)</td>
<td>59.1 (33.4)</td>
</tr>
<tr>
<td>Emotional heath</td>
<td>No (n=16)</td>
<td>60.9 (27.6)</td>
</tr>
<tr>
<td>Body image</td>
<td>Yes (n=46)</td>
<td>46.3 (24.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>No (n=16)</td>
<td>58.4 (26.6)</td>
</tr>
</tbody>
</table>

Table 6: Association between HRQOL and NSAIDS

<table>
<thead>
<tr>
<th>Variable</th>
<th>NSAIDS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical health</td>
<td>Yes (n=34)</td>
<td>51.6 (23.7)</td>
</tr>
<tr>
<td>Pain</td>
<td>No (n=28)</td>
<td>51.2 (29.2)</td>
</tr>
<tr>
<td>Planning</td>
<td>Yes (n=34)</td>
<td>58.6 (30.6)</td>
</tr>
<tr>
<td>Int. Relation</td>
<td>No (n=28)</td>
<td>39.1 (36.2)</td>
</tr>
<tr>
<td>Burden to others</td>
<td>Yes (n=34)</td>
<td>58.5 (34.6)</td>
</tr>
<tr>
<td>Emotional heath</td>
<td>No (n=28)</td>
<td>63.8 (27.6)</td>
</tr>
<tr>
<td>Body image</td>
<td>Yes (n=34)</td>
<td>47.3 (22.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>No (n=28)</td>
<td>58.3 (25.9)</td>
</tr>
</tbody>
</table>
Clinical features of lupus: The most common clinical feature in our population was arthritis/athralgia, oral ulcers, malar rash, serositis, CNS symptoms and discoid rash. At the time of being included in the study, most patients had early disease. Stefanidou et al\textsuperscript{11} in Greece found that most common clinical feature in the females was also arthritis/athralgia. Taylor\textsuperscript{12} in Zimbabwe also found the most prevalent clinical feature to be arthritis/athralgia. This was also replicated in Tunisia (78%)\textsuperscript{13} and in Nigeria by Adelowo et al (87%)\textsuperscript{14}.

Health Related Quality of Life: The study found that our population scored globally low in all the domains of the LUPUS QOL. The domain with the highest was planning 63.7(SD 29.3). Our scores could be low because the fatigue experienced by patients with lupus may prevent them from planning for future events or committing themselves to social arrangements. Some of the clinical features like pain, athralgia, oral ulcers may also limit patients appearance in public due to the altered physical appearance.

Emotional health, though it had a low score (61.3, SD 21.5), was one of our higher scoring domains. This could be because most of our patients (54%) were married and the support from the spouse could have contributed to better emotional health. Also for the single people their immediate family could have still provided them with the emotional support needed to handle their condition. The domain on burden to others was our third highest scoring domain (58.9 SD 38.2). Our population probably still had active disease, especially those with short duration of illness and had to rely on others for help with their daily activities.

Pain had a low score of 56.6. Physical health (54.0 SD 23.3). Again our patients had early disease that was probably still active. Considering that the clinical feature we found most prevalent was arthritis and athralgia present in 88.7% of our population, this could have contributed to our low scores in these two domains.

Again having scored low in pain domain and physical health, it is not surprising that intimate relations had the lowest score (41.1SD 38.4). The pain they were experiencing, poor physical health, low body image and presence of fatigue, all could have affected their desire and/or enjoyment of sexual relations.

Body image was one of the lowest scoring domains, 47.1 (SD 24.2). A large proportion of patients had mouth ulcers (62.9%) along with discoid rash and malar rash. These may have adversely altered the body image of our patients.

Fatigue is a common symptom of lupus and can sometimes present on its own for years before diagnosis of lupus is finally made. Though we did not look specifically for the presence of fatigue in our population, many studies have found fatigue to be one of the most common and most debilitating feature in lupus. Robb-Nicholson et al\textsuperscript{15} found in his study a prevalence of 81%. He also found out that most of them had active disease.

Current drug management: While the most common drug in lupus treatment is HCQ (LUMINA)\textsuperscript{16}, the most common drug in our population was prednisone with majority (74.2%) being on it. This was followed by HCQ (69.4%) then NSAIDS (54.8%). Active disease is treated by prednisone and therefore majority of our patients probably had active disease.

Azathioprine, Methotrexate (MTX), Mycophenolate Mofetil (MMF) cyclosporine is used for organ specific disease and the fact that few patients were on them may reflect the fact that few had organ specific disease, though we did not look for that in our study. Of note is that the 7(11.3%) patients using CCB were using for HTN and not for Reynaud's phenomenon. In our correlation analysis we did not find the use of any of the drugs to correlate significantly with HRQOL.

The rest of the drugs were being used by too few people to make any correlations. It was also not possible to make correlation between HRQOL and gender as there were only two men.

### Discussion

Our population mean age was 37.3 years with youngest being 14 and oldest 71. This could be because diagnosis takes time in our setting, either due to reduced awareness of the disease or due to limited laboratory and imaging tests needed to make the diagnosis. Lupus is also sometimes difficult to diagnose and even in the best of settings and the most experienced clinicians, diagnosis may still take time. Most of our patients reported they had symptoms, for up to 3 years in some, before the diagnosis of lupus was finally made.

Lupus is mostly a disease of females of child bearing age and so it is not surprising that our population of 62 had only 2 males, (M:F 1:30). Our M:F ratio was also higher than in other studies, e.g., Wadee et al\textsuperscript{8} in South Africa found a male:female ratio of 1:18. Our smaller population may account for the higher ratio in our population.

Duration of illness in our population was 1.5 years (range 1 month - 12 years), much lower than in other populations. This reflects recent advances in our healthcare with more people being aware of the disease and having better laboratory and imaging techniques required to diagnose lupus. Other studies give a longer duration of illness. Benchmark study in the US had a prevalence of fatigue in our population, this could have contributed to our low scores in these two domains.

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Correlating HRQOL with age: Positive correlation was found when HRQOL was compared with age in the domains; Burden to others, emotional health, fatigue. The study found that our patients scores in these domains increased with advance in age. Jolly et al. consistently found that advance in age correlated negatively with these domains, our population was different. A possible explanation for this could be emotional health improves in the older patients with lupus because they have had a longer duration of illness therefore they are more stable. It could also be because they may have learnt coping mechanisms by then that better help them accept their disease. Accepting and learning to cope may also have contributed to them being less of a burden to others. However a different study that looks specifically at this correlation to find out which factors directly affect these domains would be warranted to better explain these findings.

Conclusions

This study demonstrates that HRQOL in patients with lupus using the LUPUS QOL is globally found in all domains. In this study, advance in age was found to positively correlate with HRQOL in the domains of burden to others, fatigue, physical health and emotional health. There was no correlation between HRQOL and duration of illness and the drugs used.

Limitations

The cross sectional design of our study meant that it was not possible to measure any changes that may have occurred over time, as quality of life is dynamic and subject to change. The small sample size also made it impossible to do some of the correlation analysis, eg for gender and HRQOL. 

Recommendations

We recommend a study looking at the disease severity of the patients and correlating it with HRQOL. We also recommend another study looking into the specific factors in our population that would make those with more advanced age have a better HRQOL than their younger counterparts.

References

Gouty arthritis in Nigerians: clinical and laboratory correlates

Adelowo OO¹, Umar A², Oguntona SA³

Abstract

Background: Gout has been infrequently reported in black Africans despite the high prevalence in black Americans. There are even fewer reports in West Africans. However, there is a current trend towards increasing frequency among Caucasians, which is mostly due to increasing incidence of obesity, hypertension as well as the consumption of alcohol and other purine loaded foods and drinks. The increasing usage of diuretics and low dosage of aspirin may also be among the contributing factors. These factors are also increasingly been found in black Africans.

Objectives: To determine the correlation between the clinical presentations, laboratory findings and pattern of presentation of gout among Nigerians.

Design: A retrospective study.

Settings: The study was conducted at a private practice rheumatology clinic in Lagos, Nigeria. The clinic serves as a major referral rheumatology clinic for Lagos and the adjoining states.

Methods: The case notes of the patients seen over 10 years (January 2001- December 2010) were retrieved. The patients were those who met the American College of Rheumatology Criteria for gout. Data extracted included patients demography, pattern of joint involvement and co-morbid conditions. Necessary literature review was done.

Results: A total of 146 subjects were studied. Most of the patients were male (74%), the mean age for all subjects was 53.4 years. Large joints such as the knee and ankle were mostly involved. While monoarticular presentation was mostly observed in half of the subjects, oligo- and polyarticular presentations were seen in the remaining half. Tophi were observed in 6.2% of the subjects. Gout was predominantly associated with hypertension. Association was also found with obesity, diabetes, osteoarthritis and alcohol consumption to a lesser extent.

Conclusion: Gout seen in Nigerians has both similarities and differences compared to those seen in other black Africans.

Key words: Gouty arthritis, Nigerians, Associations, Clinical, Laboratory correlates

Introduction

Gout results from an abnormality of uric acid metabolism and/or secretion. It is usually characterised by hyperuricaemia which results from either overproduction of monosodium urate monohydrate or its under secretion; or often a combination of both¹. Normal blood urate concentrations vary widely among different populations. Gouty arthritis results from the deposition of monosodium urate crystals in synovial joints, soft tissues as well as elsewhere².

Gout is predominantly seen in males, but also to a lesser extent among post menopausal women. It has been reported among various populations worldwide. In USA, the prevalence is higher among African Americans than Caucasians³. There have been few previous reports of gout among black Africans, and it has mostly been said to be uncommon⁴-⁸. Recent reports may however suggest an increased frequency, especially among West Africans⁹,¹⁰. There is thus a need to determine the clinical presentation of this condition among this population.

The objective of this study was to elucidate the clinical presentations, associations and laboratory characteristics of Nigerian patients presenting with gout as well as compare the clinical features with those in other reported African studies.

Materials and Methods

This was a retrospective study of consecutive patients presenting with gout to a private practice rheumatology clinic, Arthrimed Specialist Clinic located in Lagos, Nigeria. These patients were seen over a ten year period, January 2001 to December 2010.

Patients presenting with the American College of Rheumatology
(ACR) criteria for diagnosis of gout\textsuperscript{11}, especially the clinical and laboratory characteristics were included. These are (i) presence of arthritis developing within a period of twenty-four hours. (ii) previous episodes of monoarthritis. (iii) elevated serum uric acid greater than 7mg per 100ml using Calorimetric Coulter equipment. The sensitivity and specificity of the ACR criteria compared with the gold standard of synovial fluid crystal analysis have been shown to be of the order of 70\% and 78.8\% respectively\textsuperscript{12}. Patients were subjected to complete physical examinations, including Body Mass Index (BMI) – (calculation done by weight of patient in Kg divided by height in meter square) as determined by the World Health Organisation Expert Committee\textsuperscript{13}. Blood was also taken for haematological, biochemical; as well as serology tests.

**Results**

A total of 2385 patients presenting with all musculo-skeletal complaints were seen in this clinic during the 10 year period. Out of this number, 146 were diagnosed as having gout, thus constituting 6.1\% of the total number. The demographic characteristics of the diagnosed gout patients are as shown in Table 1.

| Table 1: Demographic characteristics of 146 gout patients |
|---------------------------------|----------------|
| Total number                    | 146 |
| Male                            | 108 (74\%) |
| Female                          | 38 (26\%) |
| Age at presentation (years)     |     |
| Range                           | 38 – 90 |
| Mean(all)                       | 53.4 ± 11 |
| Mean-Male                       | 52.8±10.3 |
| Mean-Female                     | 54.9±13 |

Males were more commonly affected M:F\textsuperscript{=2.8:1}. Mean age at presentation for all subjects was 53.4±11 years with a higher mean age in women. Most of the patients had monoarthritis but there was a significant number of subjects presenting with oligoarthritis, and polyarthritis to a lesser extent as shown in Table 2.

| Table 2: Pattern of joint affection among 146 gout patients |
|---------------------------------|----------------|
| Pattern of joint affection      | Frequency (%) |
| Monoarthritis                   | 73 (50) |
| Oligoarthritis                  | 52 (35.6) |
| Polyarthritis                   | 21 (14.4) |

A total of 225 joints were affected in 146 patients. The large joints were most commonly involved and to a lesser extent the first metatarsophalangeal joint as shown in Table 3.

| Table 3: Joint affection in 146 gouty arthritis subjects |
|---------------------------------|----------------|
| Joint involvement              | No. (%) |
| Knee                            | 81 (55.5) |
| Ankle                           | 50 (34.2) |
| Hallux                          | 21 (14.4) |
| Other toes                      | 15 (10.3) |
| Wrist                           | 14 (9.6) |
| Metacarpophalangeal and proximal Interphalangeal | 13 (8.9) |
| Shoulders                       | 13 (8.9) |
| Elbow                           | 12 (8.2) |
| Hip                             | 6 (4.1) |

Nine patients (6.2\%) had tophi in various places but more over the joints of the elbow, hands and feet. Figures 1-5 show tophi on different locations with associated joint deformities.

**Figure 1:** Large tophi over the left knee in a patient with gout

**Figure 2:** Gross feet deformity and multiple tophi in a chronic gouty arthritis patient
Eighty eight patients (60.3%) had various co-morbidities with hypertension being the commonest. There were also associations with obesity, osteoarthritis and others as shown in Table 4. There was association with alcoholism in 26 (17.8%) of the subjects. Eighteen subjects (12.7%) were obese with 4 having class 1 obesity (BMI = 30 – 34.9 kg/m²); 6 subjects had class 2 obesity (BMI 35 – 39.9 kg/m²) while 8 subjects had class 3 obesity (BMI > 40kg/m²)

Table 4: Co-morbidities and associations of gout among Nigerian patients

<table>
<thead>
<tr>
<th>Risk factor/co-morbidities</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>72 (49.3)</td>
</tr>
<tr>
<td>Obesity</td>
<td>18 (12.3)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>15 (10.3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (4.1)</td>
</tr>
<tr>
<td>Lymphoproliferative disease</td>
<td>1 (0.7)</td>
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<tr>
<td>Renal failure</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Post renal transplant</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Tuberculosis of the spine on Pyrazinamide</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1 (0.7)</td>
</tr>
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</table>
Table 5: Comparative characteristics of gout among various African populations

<table>
<thead>
<tr>
<th></th>
<th>Togo Mijinyawaa</th>
<th>South Africa 1 Cassim et a18</th>
<th>South Africa 2 Mody et al18</th>
<th>South Africa 3 Tikly et al21</th>
<th>Kenya Oyoo20</th>
<th>Nigeria Adelowo et al. (Present study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>106</td>
<td>107</td>
<td>19</td>
<td>90</td>
<td>21</td>
<td>146</td>
</tr>
<tr>
<td>Male: Female</td>
<td>16.1:1</td>
<td>6.1:1</td>
<td>3.8:1</td>
<td>3.3:1</td>
<td>9.5:1</td>
<td>2.8:1</td>
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<tr>
<td>Mean age (all)</td>
<td>45.0</td>
<td>50.0</td>
<td>54.3</td>
<td>44.4</td>
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<td>52.8 (50.5)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>54.9</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of symptom (mean years)</td>
<td>8.0</td>
<td>3.1</td>
<td>3.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of joints involved (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Monoarthritis</td>
<td>59.0</td>
<td>37.4</td>
<td>26.0</td>
<td>55.6</td>
<td>47.6</td>
<td>50.5</td>
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<tr>
<td>Oligoarthritis</td>
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<td>28.0</td>
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<td>19.1</td>
<td>31.8</td>
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<td>Polyarthritis</td>
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<td>34.6</td>
<td>74.0</td>
<td>44.4</td>
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<td>14.3</td>
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<tr>
<td>Tophi (%)</td>
<td>19.0</td>
<td>47.0</td>
<td>51.1</td>
<td></td>
<td>19.1</td>
<td>6.2</td>
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<tr>
<td>Joints affected (%)</td>
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<td>Knee</td>
<td>85.0</td>
<td>79.0</td>
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<td>MTP</td>
<td>74.8</td>
<td>58.0</td>
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<td></td>
<td>14.4</td>
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<tr>
<td>Ankle/Feet</td>
<td>61.7</td>
<td>42.0</td>
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<td></td>
<td>34.4</td>
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<td></td>
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<td>1.4</td>
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<tr>
<td>MCP/PIP</td>
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<td></td>
<td>9.3</td>
<td>8.9</td>
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<tr>
<td>Elbow</td>
<td></td>
<td>26.0</td>
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<td></td>
<td></td>
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<tr>
<td>Soft tissue</td>
<td>3.0</td>
<td></td>
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<td></td>
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<td>3.4</td>
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<tr>
<td>Co-morbidities/Associations(%)</td>
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<tr>
<td>Hypertension</td>
<td>39.0</td>
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<tr>
<td>Obesity</td>
<td>38.0</td>
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<td>12.7</td>
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<tr>
<td>Diabetes</td>
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<td></td>
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<td>17.8</td>
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<tr>
<td>Osteoarthritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.4</td>
<td>10.3</td>
</tr>
</tbody>
</table>

Laboratory results: One hundred and sixteen (79.5%) had elevated uric acid above 7mg/dl at presentation. The remaining that were normouricaemic however eventually developed elevated plasma uric acid on follow-up. Range of uric acid at presentation was 2.5-14.3mg/dl with a mean of 7.9 ± 2.4mg/dl. Haematocrit at presentation was in the range of 24 – 52% with a mean of 37.6 ± 5.6. Erythrocyte Sedimentation Rate (ESR) was available in 114 patients. The values ranged between 2 – 140 mm/hr with a mean of 45.4 ± 37.6 mm/hr. Forty eight subjects (32.9%) had ESR above the normal limit of 20mm/hr. Plasma total cholesterol was available in 64 patients. Out of this, 38 (59.3%) had levels above 192mg/dl. The range was 125-402mg/dl with a mean of 211 ± 56.8md/dl. Thirty five subjects had results of plasma triglycerides available, of which only 4 (11.4%) had levels above 150mg/dl. The range of plasma triglycerides was 57-349mg/dl (mean 129.5 ± 60.3). Rheumatoid factor by latex agglutination method was available in 37 patients and all were negative.

Treatment: Treatment was with standard drugs of non steroidal anti inflammatory drugs with or without colchicine. Intra articular corticosteroids was also administered in those with knee involvement. Patients with recurrent attacks and elevated serum uric acid above 11mg/dl were given the xanthine oxidase inhibitor, allopurinol. Oral corticosteroid was not given as most patients refused or were unsuitable because of co existing co morbidities such as diabetes.

Discussion

There are increasing reports of gout in various populations worldwide, particularly in the elderly persons14. For instance, studies from USA have showed an increased prevalence of gout from 2.9/1000 persons in 1990 to 5.2 per 1000 persons in 199915. A more recent study from USA has also shown that the number of self reported cases increased from 2.1 million to 3 million over a ten year period16,17. Most of the reports from black Africa in the 60’s and 70’s have been single case reports. However from the 80’s there have been moderate numbers case series reports18-21.

Such increase in reportage is probably exemplified among Nigerians. For instance only two patients (1.4%) with gout were reported out of a total of 138
rheumatology cases seen in 1982 at a university teaching hospital. This present study found 146 subjects (6.1%) with gout out of the total of 2385 subjects presenting to the clinic in the study period. The seeming increased reports of gout in Nigerians and other black Africans or elsewhere could be attributed to various reasons such as adoption of western lifestyle and diets rich in cholesterol and purines. Other reasons could be the increased alcohol consumption, hypertension, increased usage of low dose aspirin, renal failure and obesity.

As shown in Table 5 there are both similarities and dissimilarities in the demographics and associations of gout among different black African populations. The recognized male preponderance of gout is confirmed in our study, though the male to female ratios vary widely. While our study gave a ratio of 2.8:1 similar to South African reports of 3.3:1 and 3.8:1, however reports from Kenya and Togo gave gender ratios of 9.5:1 and 16.1:1 respectively. This wide variation is difficult to explain and may be due to patient selection. The mean age at presentation in our study was 53.4 years (male – 52.8 ±10.3; female – 54.9 ±13.9). This is in consonance with the findings among other black African populations as shown in Table 5. There is, as expected, a higher mean age in females because of occurrence of gout in post menopausal women. The mean duration of symptoms before presentation in our study was 3.6 years, similar to reports in black South Africans with a mean of 3.1 years. This however contrasts to a mean of 8 years among Togolese patients. It is generally known that there is delayed hospital attendance for most diseases among black Africans. This may be due to poor utilization of health facilities, or non-affordability of hospital costs. It may also be due to the competing consultation by patients of traditional healers and other alternative practitioners.

Studies among Caucasians have always shown a dominant mono-articular gout presentation. Some reports in African blacks have shown the contrary. Half of our subjects had monoarticular presentation (50.5%) but with significant oligoarticular (31.8%) and polyarticular (14.3%) presentations. Studies from other African countries have also shown dominant polyarticular or oligoarticular presentation (Table 5). Large joints such as the knee, ankle are predominantly involved in our study with relatively less metatarsophalangeal joint involvement. This is in contrast to the predominant metatarsophalangeal joint involvement among Caucasians. Studies from South Africa have also shown predominant large joints involvements too. Soft tissue involvement of bursitis were seen in 3.4% of our patients similar to the 3% reported by Mody and Naidoo. Tophi were seen in only 6.2% of our patients and they were mostly over the elbow joints. Some of the tophi were, however, large and deforming (Figures 1-4). Our study showed a lower frequency of tophi than reported from elsewhere in Africa.

The associations and co-morbidities of gout are as reported elsewhere, with hypertension occurring significantly (Table 5). There have been reports of high association of gout and hypertension in black African Americans. Other associations include obesity (12.3%); osteoarthritis (10.3%); dyslipidaemia (10.3%). These associations have also been reported variously from other African studies. A significant departure from other reports however is the rather low frequency of association with alcohol. In our patients, 4.1%; in contrast to 74% in Togo and 100% in Kenya as well as South Africa. This may be attributable to differences in religious and social influences. Of particular note is the association of gout with osteoarthritis in our study. It has been suggested that the tissue changes in osteoarthritis may encourage local deposition of monosodium urate crystals in the joints involved, hence such association. As seen in Table 4, other associations of gout in our study includes lymphoproliferative disease, renal failure, post renal transplant, and psoriatic arthritis. Co existing gout and rheumatoid arthritis was seen in one of our patients. There has been a previous report of this association in a Nigerian. However such coexisting rheumatoid arthritis and gout have been reported as being rare.

Most of our subjects (79.5%) had elevated uric acid level at presentation, although others had elevation during subsequent visits. It is well recognised that elevated uric acid may not be a reflection of an acute attack and may in fact be normal. This has been attributed to the triggering of the acute phase response and an accompanying urinary urate excretion. The associations and co-morbidities of gout are as reported elsewhere, with hypertension occurring significantly (Table 5). There have been reports of high

Acknowledgements

The authors will like to thank the clinic nurse, Mrs Irene Oduenyi for sorting out the case files and laboratory results. We also thank Adem and Pathcare Laboratories for blood tests.
References

Prevalence of gastroduodenal lesions in chronic non-steroidal anti-inflammatory drug users presenting with dyspepsia at the Kenyatta National Hospital

Wanjohi W, Ogutu E, Oyoo GO, Kioko HM, Radia K, Mutie TM

Abstract

Background: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are among the most widely prescribed and used classes of drugs worldwide. They are known to cause gastroduodenal mucosal damage and can result in ulcerations, upper gastrointestinal bleeding, perforation and even death. However, no local data exist to show the prevalence.

Objectives: The main objective was to determine the prevalence of gastroduodenal lesions seen at endoscopy and histopathology in chronic NSAID users presenting with dyspepsia at the Kenyatta National Hospital.

Design: This was a hospital-based cross-sectional study.

Methods: Seventy patients aged 13 years and above, on NSAIDs for 4 weeks or more, and presenting with dyspepsia were recruited and done for endoscopies. Six biopsy specimens were taken from each patient (2 from each of the following sites: corpus, antrum and duodenum). One specimen from each site was subjected to the rapid urease test for \( H. pylori \) detection. The remaining three were subjected to histopathological evaluation.

Results: Forty male and 25 female patients aged between 16-77 years, with a mean age of 43.4 years were studied. At endoscopy, only 10 (13.9%) patients had normal gastroduodenal mucosa. Gastritis was the most prevalent lesion occurring in 50% of the patients. Peptic ulcer disease had a point prevalence of 30.5% (duodenal ulcers 22.2%, and gastric ulcers 8.3%). Other lesions at endoscopy were duodenitis 16.7%, gastric erosions 5.6%, duodenal erosions 1.4% and hemorrhagic gastritis 1.4%.

At histopathology, only 5 (6.9%) patients had normal gastroduodenal mucosa. Chronic active gastritis was the most prevalent lesion at 77.8%. Other lesions were chronic gastritis 12.5%, chemical gastritis 6.9%, duodenitis 41.7% and intestinal metaplasia 4.2%.

Prevalence of \( H. pylori \) in our study population was 50%. There was no association between the gastroduodenal lesions and \( H. pylori \) infection.

Conclusions: There was a high prevalence of gastroduodenal mucosal lesions both at histopathology (93.1%) and endoscopy (86.1%) in the chronic NSAID users.

Introduction

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are commonly used drugs and can cause gastroduodenal mucosal damage, from non-specific dyspepsia, ulcerations, upper gastrointestinal bleeding, perforation, to death\(^1\). No data exists to show the prevalence of these lesions in our local setting.

The main objective was to determine prevalence of gastroduodenal lesions in chronic NSAID users with dyspepsia, in Kenyatta National Hospital, Nairobi, Kenya. The other objectives included describing the lesions seen at endoscopy and the histopathological characteristics. The study also sort to find out the relationship between duration of NSAID use, previous peptic ulcers and UGI bleed (UGIB) and the gastroduodenal lesions. Finally the study sort to find out any differences in the gastroduodenal lesions seen at endoscopy and histopathology in chronic NSAID users with and without \( H. pylori \) infection.

Materials and Methods

This was a cross-sectional, descriptive study done at KNH endoscopy unit. Patients aged over 13 years, with musculoskeletal disorders requiring chronic NSAID therapy with or without acute upper GI events (UGI bleed and / or perforation) were eligible. Those excluded were patients who had been treated for \( H. pylori \) infection, antibiotic use in the preceeding month, patients on gastroprotective drugs (PPIs, \( H_2 \)-antagonists, misoprostol), for more than two weeks preceeding endoscopy, use of selective COX-2 inhibitors and patients...
of Asian and Caucasian descent. Eighty two patients on chronic NSAID use were found eligible. Seventy five of these gave informed and written consent, and 72 of them had a successful upper GI endoscopy.

**Results**

*Demographic and clinical details of the study patients:* The mean age of the patients was 43.4 years, youngest being 16 and the oldest 77 years. Most patients were aged 21–40 years representing 51.4% of the total population. (Table 1) m: f 1.88: 1.

Table 1: Clinical details of the patients (n=72)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frequency</th>
<th>(%)</th>
</tr>
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<tbody>
<tr>
<td>Duration of NSAID use (in months)</td>
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<td></td>
</tr>
<tr>
<td>1 to 3</td>
<td>41</td>
<td>56.9</td>
</tr>
<tr>
<td>&gt; 3</td>
<td>31</td>
<td>43.1</td>
</tr>
<tr>
<td>History of PUD</td>
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</tr>
<tr>
<td>Yes</td>
<td>5</td>
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</tr>
<tr>
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<td>History of UGIB</td>
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</tr>
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<td>Yes</td>
<td>8</td>
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<td>88.9</td>
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<td>57</td>
<td>79.2</td>
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</tbody>
</table>

Mean age of males was 42.5 years (SD ± 16.5), females was 45.1(SD ± 15.7). Ten (13.9%) of those on gastroprotective drugs used PPIs while eight (11.1%) used H$_2$-receptor antagonists. Of these, five had previous UGIB, three had previous PUD. Four of those with previous UGIB and one of those with previous PUD were on PPIs. Three of those over 60 were on gastro-protective drugs. NSAIDs commonly used were diclofenac (52%) and ibuprofen (26%). Forty one (61.1%) had used only one NSAID, 16 (22.2%) had switched from one type to another, while 12 (16.7%) were on more than one type.

*Prevalence of gastroduodenal lesions at endoscopy:* Figure 1 shows gastroduodenal lesions at endoscopy. Four patients had three lesions at endoscopy while 13 had two. Six of the patients with duodenitis also had gastritis, whereas eight of those with peptic ulcers, had gastritis. Gastritis was the most prevalent lesion (36 cases) (Figure 2).

**Figure 1:** Prevalence of gastroduodenal lesions at endoscopy

**Figure 2:** Distribution of gastritis
Table 2: Endoscopic findings according to previous history of PUD and UGIB

<table>
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<tr>
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<th>Prior PUD (n = 5)</th>
<th>No prior PUD (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
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<tr>
<td>Normal</td>
<td>-</td>
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</tr>
<tr>
<td>Gastritis</td>
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<td>4 (6.0)</td>
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<td>Gastric</td>
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<td>Gastric mass</td>
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<tr>
<td>Hemorrhagic gastritis</td>
<td>-</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endoscopic findings</th>
<th>Prior UGIB (n = 8)</th>
<th>No prior UGIB (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Normal</td>
<td>-</td>
<td>10 (15.6)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>3 (37.5)</td>
<td>33 (51.6)</td>
</tr>
<tr>
<td>Gastric erosions</td>
<td>1 (12.5)</td>
<td>3 (4.7)</td>
</tr>
<tr>
<td>Peptic ulcers</td>
<td>2 (25.0)</td>
<td>20 (31.3)</td>
</tr>
<tr>
<td>Gastric</td>
<td>-</td>
<td>6 (9.4)</td>
</tr>
<tr>
<td>Duodenal</td>
<td>2 (25.0)</td>
<td>14 (21.9)</td>
</tr>
<tr>
<td>Duodenal erosions</td>
<td>1 (12.5)</td>
<td>11 (17.2)</td>
</tr>
<tr>
<td>Duodenal erosions</td>
<td>-</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Gastric mass</td>
<td>-</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Hemorrhagic gastritis</td>
<td>1 (12.5)</td>
<td>-</td>
</tr>
</tbody>
</table>

Peptic ulcer disease at endoscopy: A point prevalence of 30.5% of PUD in chronic NSAID users presenting with dyspepsia. Sixteen were males (point prevalence of 34%), 12 duodenal, 3 antral and 1 fundal. Six were found in females, (point prevalence of 24%) 4 duodenal, 2 antral. The highest frequency of PUD occurred in 41-50 years age-group, with a mean age of 44 while those without was 42 years. Fourteen patients with peptic ulcers had used NSAIDs for 1-3 months, with the remaining 8 using for longer period. However, there was no significant association with the finding of PUD at endoscopy (p = 0.585). Fourteen patients with PUD had H. pylori infection, while 8 didn’t (p = 0.125). Table 3 shows relationship between duration of NSAID use and lesions found at endoscopy and Figure 3 shows the histological distribution of the lesions. Table 4 shows the distribution of lesions in those with and without H. pylori infection.

Table 3: Relationship between duration of NSAID use and the gastroduodenal lesions at endoscopy

<table>
<thead>
<tr>
<th>Endoscopic findings</th>
<th>1-3 months (n = 41)</th>
<th>More than 3 months (n = 31)</th>
<th>P-value</th>
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<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>4 (9.8)</td>
<td>6 (19.4)</td>
<td>0.244</td>
</tr>
<tr>
<td>Gastritis</td>
<td>19 (46.3)</td>
<td>17 (54.8)</td>
<td>0.475</td>
</tr>
<tr>
<td>Gastric erosions</td>
<td>3 (7.3)</td>
<td>3 (9.7)</td>
<td>0.453</td>
</tr>
<tr>
<td>Peptic ulcers</td>
<td>14 (34.1)</td>
<td>8 (25.8)</td>
<td>0.447</td>
</tr>
<tr>
<td>Gastric</td>
<td>4 (9.7)</td>
<td>2 (6.4)</td>
<td>0.615</td>
</tr>
<tr>
<td>Duodenal</td>
<td>10 (24.4)</td>
<td>6 (19.4)</td>
<td>0.611</td>
</tr>
<tr>
<td>Duodenal erosions</td>
<td>8 (19.5)</td>
<td>4 (12.9)</td>
<td>0.456</td>
</tr>
<tr>
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<td>1 (2.4)</td>
<td>-</td>
<td></td>
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<tr>
<td>Hemorrhagic gastritis</td>
<td>1 (2.4)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Differences in gastroduodenal lesions seen in patients with and without H. pylori infection at endoscopy

<table>
<thead>
<tr>
<th>Endoscopic findings</th>
<th>Total</th>
<th>H. pylori +</th>
<th>H. pylori -</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>10</td>
<td>2</td>
<td>8</td>
<td>0.21 (0.04-1.04)</td>
<td>0.041</td>
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<tr>
<td>Gastritis</td>
<td>36</td>
<td>22</td>
<td>14</td>
<td>0.4 (0.16-1.0)</td>
<td>0.059</td>
</tr>
<tr>
<td>Gastric erosions</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1.0 (0.13-7.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Peptic ulcers</td>
<td>22</td>
<td>14</td>
<td>8</td>
<td>0.45 (0.16-1.3)</td>
<td>0.125</td>
</tr>
<tr>
<td>Gastric</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>1.0 (0.10-5.3)</td>
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<tr>
<td>Duodenal</td>
<td>16</td>
<td>11</td>
<td>5</td>
<td>2.73 (0.84-8.9)</td>
<td>0.089</td>
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<tr>
<td>Duodenal erosions</td>
<td>12</td>
<td>8</td>
<td>4</td>
<td>2.3 (0.6-8.4)</td>
<td>0.206</td>
</tr>
<tr>
<td>Gastric mass</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hemor. gastritis</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
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</table>
Afr J Rheumatol 2014; 2(1): 29-34

make any conclusions. It was also a significant finding in
(p = 0.035). However, our numbers were too small to
the previous PUD (p = 0.023). However, the
numbers were again too small to make any significant
conclusions. The relative risk of finding any abnormal
histological diagnosis for PUD and UGIB was 0.3 and
0.52 respectively.

Relationship between duration of NSAID use and
histopathological findings: Duodenitis was significant in
patients who had used NSAIDs for 1-3 months (p=0.004).

Histological findings versus H. pylori infection: Normal
gastroduodenal mucosa was noted in those without
H. pylori infection. Of the five patients with a histological
diagnosis of normal mucosa, none had H. pylori
infection. Finding of chronic gastritis was significant
in those without H. pylori infection. (p=0.013, OR 0.1
95%CI 0.01-0.8). Chronic active gastritis was significant
in those with H. pylori infection. (p-value < 0.001, OR =
25.0 (95% CI 3.1-203.2). However, no other lesions were
significant in the presence of H. pylori.

Discussion

NSAID associated gastrointestinal toxicity encompasses
symptoms from mild to severe complications. Most data
on this topic has been obtained from studies done in the
West.

The mean age of our patients was 43.4 ± 16 years. Use
of NSAIDs increases with age, with the point prevalence
of NSAID use being 10-15% in those over 65 years.
Frezza et al found the mean age of patients was 66.5
years. Our population had relatively younger patients
because most had complicated traumatic conditions. In
other studies, most patients had arthritis. We also had a
male:female ratio of 1.88:1. This reflected the patients
admitted with traumatic and other orthopaedic conditions
at KNH surgical wards during recruitment.

Despite all patients having dyspeptic symptoms, only
18(25%) of them had used gastroprotective drugs for at
least two weeks prior to endoscopy. Most patients with
previous PUD and UGIB were on gastroprotective drugs.
Five of the eight patients with previous UGIB and three of
those with previous PUD were on gastroprotective drugs.
American College of Gastroenterology recommends use
of gastroprotective drugs especially in patients at high
risk for NSAID-related gastrointestinal complications.

At endoscopy, the most prevalent lesion was gastritis
(3(50%) (Figure 1). Our results contrast sharply with
those of Larkai et al who evaluated endoscopic
appearance of the gastroduodenal mucosa in 65 patients
on NSAIDs for at least 6 weeks. Twenty one (32%) had
an endoscopically normal stomach and duodenum, and
44(68%) had evidence of injury. Only 10 patients in their
series had ulcers detected (7 gastric, 2 pyloric channel
and 1 duodenal bulb), point prevalence of 15.4%.

These differences may be due to a lack of standard
definitions of injury. While endoscopy studies provide
valuable information, endoscopic endpoints are
subjective and need to be appropriate to the type of study.

Table 5 further breaks down the histological findings
in those who had a history of PUD and UGIB. Chronic
active gastritis was significant in patients with no
history of PUD compared to those with previous PUD
(p = 0.035). However, our numbers were too small to
make any conclusions. It was also a significant finding in
those without previous UGIB, (p-value = 0.045). Whereas
chronic gastritis was a significant finding in those with
a previous history of UGIB (p = 0.023).

Table 5: Histological findings according to history of
PUD or UGIB

<table>
<thead>
<tr>
<th>Histological findings</th>
<th>History of PUD</th>
<th>History of UGIB</th>
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</thead>
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<tr>
<td></td>
<td>Prior PUD</td>
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</tr>
<tr>
<td></td>
<td>(n = 5)</td>
<td>(n = 67)</td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Normal</td>
<td>1 20.0</td>
<td>4 6.0</td>
</tr>
<tr>
<td>Chronic active gastritis</td>
<td>2 40.0</td>
<td>54 80.6</td>
</tr>
<tr>
<td>Chronic gastritis</td>
<td>1 20.0</td>
<td>8 11.9</td>
</tr>
<tr>
<td>Duodenitis</td>
<td>2 40.0</td>
<td>28 41.8</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>- -</td>
<td>3 4.8</td>
</tr>
<tr>
<td>Chemical gastritis</td>
<td>- -</td>
<td>8 11.9</td>
</tr>
<tr>
<td>Glandular atrophy</td>
<td>- -</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 3: Prevalence of gastroduodenal lesions at
histopathology

Histopathologic diagnosis

Unlike endoscopy where 10 (13.9%) patients were found
to have normal gastroduodenal mucosa, only 5(6.9%)
had normal mucosa at histopathology. Many patients
had more than one histological finding. Eight patients
had three mucosal lesions concurrently histologically
while 28 had two mucosal lesions. Twenty three (31.9%)
patients with chronic active gastritis also had duodenitis.
Three (4.2%) with chronic active gastritis also had
gastritis, while all the 3(4.2%) patients with
intestinal metaplasia had chronic active gastritis.
Our study was designed to study the chronic endpoints. All published studies have proposed confounders that may increase the risk of NSAID associated adverse gastrointestinal events\textsuperscript{2,9}. These include:- previous PUD, previous UGIB\textsuperscript{10,11} above 60 years\textsuperscript{11}, alcohol and cigarette smoking,\textsuperscript{2} duration of NSAID use,\textsuperscript{12} use of $\geq 2$ NSAIDs, high doses,\textsuperscript{10} and use of corticosteroids and anticoagulants\textsuperscript{13}. Previous PUD and UGIB and duration of NSAID use, showed no significant association with the lesions at endoscopy ($p > 0.05$). Other studies published show the relationship between chronic NSAID use and mucosal colonization by $H.\ pylori$ reported a lower prevalence of $H.\ pylori$ in the gastric mucosa of chronic NSAID users\textsuperscript{14,15}. It’s thought the gastric environment created by NSAIDs might be unfavorable to $H.\ pylori$ implantation, confirmed by the fact that NSAIDs can block the growth of bacterium in vitro\textsuperscript{16}. However, other studies reported an equal prevalence of $H.\ pylori$ in chronic users and control groups\textsuperscript{17}. Our prevalence of $H.\ pylori$ was 50%, lower than in studies conducted locally in dyspeptic patients in the general population. Lwai-Lume et al\textsuperscript{18} reported a prevalence of 69% in a population where only two patients were on NSAIDs. It may be possible that NSAIDs impair implantation and growth of $H.\ pylori$ in the gastroduodenal mucosa, hence the lower prevalence in our population.

The relation between $H.\ pylori$ and NSAIDs use in pathogenesis of gastroduodenal lesions is controversial. Both $H.\ pylori$ infection and NSAIDs were independently and significantly found to increase the risk of peptic ulcers and ulcer bleeding\textsuperscript{19}. Several studies have shown that $H.\ pylori$ doesn’t influence the endoscopic grade of mucosal lesions in long-term users\textsuperscript{6}. In our patients, the finding of a normal gastroduodenal mucosa was significant in those without $H.\ pylori$ infection ($p=0.041$, OR 0.21 95% CI 0.04-1.04). However, no lesions were significant in the presence of $H.\ pylori$.

NSAIDs have been associated with a high prevalence of gastroduodenal ulcers, either by the presence of $H.\ pylori$ and/or the mucosal damage now thought to present as chemical gastritis\textsuperscript{20}. The point prevalence of PUD in our patients was 30.5%. $H.\ pylori$ infection was present in 14 of the 22 patients with peptic ulcers at endoscopy. While those with $H.\ pylori$ had more ulcers than those without it or chemical gastritis, this wasn’t significant ($p=0.125$). Lwai-Lume et al\textsuperscript{18} reported a point prevalence of PUD of 23% (19% duodenal, 4% gastric) from the general population. These duodenal ulcers were significantly associated with $H.\ pylori$ infection whereas gastric ulcers weren’t. There may be a synergistic effect between NSAIDs and $H.\ pylori$ in causing gastroduodenal damage, but it seems that in some cases, NSAIDs may have been responsible for producing the lesions via different pathways. NSAIDs may damage the mucosa via inhibition of prostaglandins synthesis\textsuperscript{21} and functional impairment of the mucosal barrier\textsuperscript{22}. These may explain those ulcers found in the $H.\ pylori$ negative cases.

Using the Updated Sydney System\textsuperscript{23}. Only 6.9% of our patients had chemical gastritis. The prevalence of chemical gastritis in chronic NSAID users is variable. El-Zimaity et al\textsuperscript{24} proposed various reasons, considering that of all those regularly taking NSAIDs, few (with greater sensitivity) develop chemical gastritis, and mucosal damage may be patchy.

In our patients, the finding of a normal gastroduodenal mucosa and chronic gastritis ($p=0.013$) was significant in patients without $H.\ pylori$. Chronic active gastritis was also significant in those with $H.\ pylori$ ($p < 0.001$, OR 25 95% CI 3.1-203.2). Thirty five of the 56 with chronic active gastritis had $H.\ pylori$. $H.\ pylori$ and NSAIDs seem to act independently in causing gastroduodenal lesions in chronic NSAID users.

Three patients with chemical gastritis also had chronic active gastritis. Two also had $H.\ pylori$ infection. The Updated Sydney System stresses that a patient may have histopathological evidence of more than one type of gastritis due to exposure to more than one aetiological agent. Our patients had gastritis due to chronic NSAIDs ingestion (chemical gastritis) and chronic active gastritis associated with $H.\ pylori$ infection.

Though only three patients had intestinal metaplasia, only two were above 50 years ($p=0.046$). All three patients had used NSAIDs for $> 3$ months. One had concurrent $H.\ pylori$ infection, none was on gastroprotective drugs. Intestinal metaplasia is common in chronic gastritis and it predisposes to malignancy, especially for lesions with large intestinal characteristics (Type III metaplasia). Elderly patients on chronic NSAIDs use, may have higher risk of intestinal metaplasia.

Previous PUD or UGIB has been shown to magnify the risk of NSAID associated gastroduodenal complications\textsuperscript{25}. Those with previous upper gastrointestinal events, had less chronic active and chronic gastritis than those without. This was an interesting observation, since the recurrence of upper gastrointestinal events have been postulated to be from mucosal changes from previous ulcer sites, with a strong tendency for lesions to relapse in the same location and of the same type\textsuperscript{26}.

Intestinal metaplasia was significant in patients who had used NSAIDs for $> 3$ months ($p=0.042$) whereas duodenitis was significant in patients who had used NSAIDs for 1-3 months ($p=0.004$). The finding of duodenitis in patients using NSAIDs for short durations hasn’t been reported in other studies and therefore needs further evaluation.

The study found a poor correlation between histopathologic and endoscopic findings of gastritis and duodenitis. Gastritis was in 91.7% of histopathology specimens, yet only 50% was reported at endoscopy. Duodenitis was reported in 41.7% of histopathology specimens only 16.7% at endoscopy. These results are in keeping with previous studies\textsuperscript{27,28}.

**Conclusions**

We have a high prevalence of gastroduodenal lesions in chronic NSAID users presenting with dyspepsia (81.6% at endoscopy, 93.1% at histopathology), with the prevalence of PUD (30.5%) being much higher than that in dyspeptic patients drawn from the general population (23%), at the Kenyatta National Hospital. Both $H.\ pylori$
References


Low back pain among patients attending rheumatology clinic in the South West Nigeria

Oguntona SA¹, Adelowo OO², Edunjobi SA³

Abstract

Background: Back pain is among the common musculoskeletal complaints for patients seeking medical care. Back pain encompasses a spectrum of conditions, those with acute and short duration, to life-long disorders. Generally, causes of back pain include osteoarthritis (spondylosis), disc degeneration, osteoporotic fracture, and non-specific low back pain.

Objective: To determine the pattern of low back pain among the people living in the South West Nigeria.

Design: Prospective study.

Methods: All the patients that presented with low back pain either with or without neuro-vascular complaints were enlisted in the study. The study was carried out over three years (January 2010-December 2012). Inclusion criterion was non-traumatic back pain. Exclusion criteria included traumatic back pain, malignancy related back pain, and inflammatory back pain.

Results: Seventy three patients were seen over three years constituting 21.7% of total rheumatology cases seen over this period. There were 45 (61.6%) males, and 26 (38.4%) females with a male: female ratio of 1.6:1. Age range was 18 to 72 years, with means of 28 years. Males were generally affected with back pain more than females. Males in their active years were more affected. Non-specific back pain was the leading cause of back pain among the patients studied.

Conclusion: The finding of non-specific low back pain as the leading cause of low back pain in this study agrees with earlier literatures on the same issue.

Keywords: Low back pain, Musculoskeletal complaint, Hospital patients, Nigeria

Introduction

Low back pain is usually defined as pain, muscle spasm, or stiffness localized below the costal margin and above the inferior gluteal folds, with or without leg pain (Sciatica). It is typically classified as being specific or non-specific. Approximately 90% cases of back pain have no identifiable cause and are designated as non-specific. The probability that a particular case of back pain has a specific cause identified on back radiograph is less than 1%. Presently, there is no reliable and valid classification system for low back pain. Acute and sub-acute pain episodes which may last up to three months are the most common presentations of low back pain. Recurrent bouts of such episodes are the norm. Chronic back pain on the other hand is more disabling because of the physical impediments it causes and its psychological effects. Low back pain is associated with multiple risk factors, including gender, age, lifestyle, psychosocial profile, and physical demand of the workplace.

Aside pain medications, interventions based on behavioral and cognitive principles, and exercise programmes are effective in improving disability of chronic back pain. Prognosis of back pain is influenced by drug therapies, patient educational materials, and sleeping materials.

The aims of this study were to determine the frequency of occurrence of low back pain as related to age and sex, and the common aetiological causes of low back pain among patients attending rheumatology clinic.

Materials and Methods

The studied groups of people were the patients who attended a private rheumatology clinic in the South West of Nigeria with history of low back pain. Inclusion criteria included non-traumatic low back pain and absence of malignancy. Excluded from the study were patients with traumatic back pain, patients with satellite malignancy, and...
people with inflammatory back pain. All patients who met the inclusion criteria were enlisted in the study. Their personal data were obtained and documented.

Plain lumbosacral X-ray with postero-anterior, and lateral view were requested in all the patients and interpreted by a radiologist. Computerized tomography, and magnetic resonant imaging were requested in patients with neuro-vascular presentations where patients were able to afford it. Bone densitometry however was not requested for in any of the patients because of non-availability locally. Haematology investigations request were made to rule out other causes of back pain.

**Results**

Seventy three cases of low back pain were seen over three years (January 2010- December 2012). This represented 21.7% of all rheumatology cases seen over this period. Males constituted 45 (61.6%) of all cases of low back pain and females made up of 28 (38.4%) with a male: female ratio of 1.6:1. Age range of patients seen was 18 to 72 years with mean age of 28 years. People below 30 years made up of 45 (61.6%) of the total patients with low back pain. Patients with features of lumbar spondylosis were 25 (34.2%), with 14 (56%) males and 11 (44%) females. There were 6 (8.2%) cases of disc herniation and 4 (5.5%) cases of spondylolisthesis (Table 1).

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Condition</th>
<th>No.</th>
<th>Male (%)</th>
<th>Female (%)</th>
</tr>
</thead>
<tbody>
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<td>1.</td>
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<td>104</td>
<td>32</td>
<td>72</td>
</tr>
<tr>
<td>2.</td>
<td>Rheumatoid arthritis</td>
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<td>4</td>
<td>8</td>
</tr>
<tr>
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<td>Cervical spondylosis</td>
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<td>23</td>
<td>13</td>
</tr>
<tr>
<td>4.</td>
<td>Low back pain</td>
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<tr>
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<td>Lumbar spondylosis</td>
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<td>11</td>
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<tr>
<td></td>
<td>Disc herniation</td>
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<td>4</td>
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<tr>
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<td>1</td>
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<td>12</td>
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<td>5.</td>
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<td>22</td>
<td>6</td>
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<td>5</td>
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<td>2</td>
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<tr>
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<td>Archilis tendinitis</td>
<td>8</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>336</td>
<td>160</td>
<td>176</td>
</tr>
</tbody>
</table>
Table 2: Demographic characteristic of low back pain patients (n = 73)

<table>
<thead>
<tr>
<th>Total number of patients</th>
<th>73</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>45 (61.6%)</td>
</tr>
<tr>
<td>Female</td>
<td>28 (38.4%)</td>
</tr>
<tr>
<td>Age range</td>
<td>18-72</td>
</tr>
<tr>
<td>Mean age</td>
<td>28 years</td>
</tr>
</tbody>
</table>

Table 3: Disorders causing low back pain in the studied patients

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spondylosis</td>
<td>14</td>
<td>11</td>
<td>25</td>
<td>34.2</td>
</tr>
<tr>
<td>Disc herniation</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td>8.2</td>
</tr>
<tr>
<td>Spondylolisthesis</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>5.5</td>
</tr>
<tr>
<td>Non-specific back pain</td>
<td>26</td>
<td>12</td>
<td>38</td>
<td>52.1</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>26</td>
<td>73</td>
<td>100</td>
</tr>
</tbody>
</table>

Non-specific low back pain constituted the bulk of the cases seen, representing 52.1% of total cases of low back pain. There were 26 (68.4%) males and 12 (31.6%) females in the non-specific back pain group as shown in Table 3. Table 2 shows demographic characteristic of 73 low back pain patients. It was however difficult to determine how many patients progressed to chronicity because of loss to follow-up.

Discussion

Low Back Pain (LBP) is the most prevalent musculoskeletal condition and the highest cause of disability. The mean age of onset of low back pain in this studied group was 28 years which is a little lower than findings in most literatures. The difference may possibly be adduced to the manual labour engaged in by most of our patients. Cross-sectional data demonstrated that initial onset of lower back pain is expected to occur around the mean age of 30 years9, and peaking in occurrence between the ages of 45 and 60 years10,11.

However, low back pain is common in both older and younger adults. Nyland and Grimmer in 200312 stated that an early emergence of lower back pain and the increase duration of suffering may go so far as to decrease performance of duties in any physically active vocation.

Low back pain is a very frequent occurring condition among the general population. Among adults, 70-85% was believed to experience at least one episode of low back pain at some time during their lives13. Anecdotally, there is a general belief that low back pain complaint is commoner in Caucasians than Africans possibly because of compensation claims by the western world14.

Men were more affected than women in this study. some authors were of the opinion that this is most likely due to hard labour engaged in by men in our society and also possibly related to prolonged sitting associated with driving. Recent studies have reported contradictory results on sex and back pain. In her review of the literature, Riihimäki15 did not report sex as a risk factor for low back pain. Also in the review by Burdorf and Sorock16, sex did not seem to be linked with low back pain. In the study of Park et al17, low back pain occurred more often among women except for low back pain caused by occupational injuries or occupational repetitive activities.

Non-specific low back pain was the commonest cause of back pain in this study. This finding however corresponded with most literatures. This is the most common type of back pain. About 19 in 20 cases of acute (sudden onset) low back pain are classed as non-specific. This is the type of back pain that most people will have at some point in their life. It is called non-specific because it is usually not clear what is actually causing the pain. In other words, there is no specific problem or disease that can be identified as to the cause of the pain18.

Low back pain is an integral part of most human lives and causes different degree of suffering and disability. The natural history of back pain seems in general to be favourable, but long-term or permanent disability should also be kept in view. Studies have found that the presence and severity of low back pain is associated with several socio-demographic factors; among them are sex, age, educational level, smoking and occupation19,20. One study of young adolescents and young adults aged 12-22 years demonstrated an overall prevalence of low back pain of 7%21 (pain greater than 30 days during the past year).

It was difficult to do a long term follow up of our patients because of high rate of loss to follow up, either because they were symptomatically better or sought alternative source of treatment. Because of the drop-out, it was difficult to determine what percentage of people who presented with acute pain progressed to chronic low back pain. However, a recent review to investigate the long-term course of incidence and prevalence cases of low back pain showed that the reported proportion of patients who still experience pain after 12 months was 62% (range 42-75%)22. Prospective studies demonstrated that low back pain do not display a six-week spontaneous recovery pattern, as was once believed23. The condition is regularly seen to worsen over time, becoming a chronic disorder, influenced by both physical and psychosocial factors24,25.
Data from general practice has also shown that a considerable proportion with low back pain continue to experience both symptoms and varying degree of disability at 4 years, although they were not necessarily seeking care at that point\textsuperscript{26}. A recently published systematic review of prospective cohort studies found that psychological factors are associated with increased risk of chronic low back pain, and also predict long-term work absence in disabling low back pain\textsuperscript{27,28}.

Low back pain can interfere with activities ranging from the basic activities of daily living to many work-related functions. In patients with acute and sub-acute low back pain, there may be unnoticeable changes in disability on quality of life\textsuperscript{29}. In chronic low back pain however, psychological distress in the form of depressive symptoms do set in and this affects the quality of life of the individual\textsuperscript{29}.

Low back pain cut across all occupations in the studied group. Students, artisans, civil servants, farmers, and traders were all affected. Of note however in this study, was the high rate of non-specific low back pain in people below 30 years. Men constituted the greater proportion of this group \(26\% (68.4\%)\). This is not however surprising, because this group represent the sexually active group, which the authors believe could have contributed to the high number.

The short coming of this study was that only hospital based patients were considered, because there are so many other people in the community with history of low back pain who visit other sources of medical care, such as traditional healers, pharmacy shops and general practitioners.

**Conclusion**

The frequency of back pain obtained in this specialist setting cannot be a true representation of the community. The frequency of low back pain obtained cannot therefore be generalized. Therefore, further research in the community will be necessary to determine the true frequency of low back pain in our community.

**Acknowledgements**

The authors wish to acknowledge the matron of the clinic, Mrs Tijani Tawakalitu, and other staff who made the data collection possible. Authors acknowledge the great help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors / editors / publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

**References**


Potential role of infliximab therapy in twelve Libyan patients with Behçet’s disease

Basma E1, Rajab T1, Amani M1, Borhan E2, Gamal B2, Eshabani M3

Abstract

Background: The blocking of tumour necrosis factor-α (TNF-α) with so-called anti TNF-α agents has turned into the most important tool in the management of a variety of autoimmune disorders.

Objective: To evaluate the therapeutic effect of infliximab on ocular and extraocular manifestations in patients with Behçet’s disease (BD).

Methods: Twelve patients with active BD who were treated with infliximab at Tripoli Medical Center for more than 6 months were included in this study. Infliximab was initiated with 5mg/kg of body weight. Infusion given at (week 0, 2, 6 and every 8 week thereafter) as either first-line therapy in eight patients or given after failure of conventional immunosuppressants in the remaining four patients. All patients were assessed by clinical examination and inflammatory markers. The patients with ocular involvement were assessed clinically by an ophthalmologist every 2 months and those with neuro- Behçet’s disease had in addition MRI assessment for the brain.

Results: The follow-up period after initial introduction of infliximab ranged from 6 to 36 months (mean±SD,15.5±7.4 months). Eight (67%) patients achieved remission without any relapse while two (17%) patients had only one relapse in the same organ during the period of follow up. One (8%) patient had relapse in another system and infliximab was stopped. One (8%) other patient had no response. Immunosuppressants were stopped in all patients except one and all were kept on low dose glucocorticoids. No drug side effects were reported. In eight patients who started on infliximab as first line therapy, the remission occurred in six patients (75%) while in the other four patients who were taking infliximab after failure of conventional immunosuppressants, the remission occurred in two patients (50%).

Conclusion: Infliximab is effective in inducing remission of BD. The good effect together with excellent tolerability suggests that infliximab can be used as first line drug in BD.

Keywords: Anti TNF-α, Infliximab, Behçet’s disease

Introduction

Behçet’s disease is an immune-mediated multisystem occlusive vasculitis of small blood vessels, especially venules, of unknown aetiology. Formerly representing a disease of typically Mediterranean origin, Behçet’s disease is now recognized in patients of various ethnicities all over the world, making it necessary to think about ‘typical’ disease manifestations in ‘atypical’ patients. The manifestations of Behçet’s disease may occur at many sites throughout the body. However, the disease seems to target certain organs and tissues. Ocular involvement can develop early in the disease course and lead to permanent vision loss in 20% of cases. Ocular involvement can be in the form of posterior uveitis, anterior uveitis, or retinal vasculitis. Anterior uveitis presents with painful eyes, conjunctival redness, hypopyon, and decreased visual acuity, while posterior uveitis presents with painless decreased visual acuity and visual field floaters. A rare form of ocular involvement is retinal vasculitis which presents with painless decrease of vision with the possibility of floaters or visual field defects.

Neurological involvement most often occurs as a chronic meningoencephalitis. Lesions tend to occur in the brainstem, the basal ganglia and deep hemispheric white matter and may resemble those of multiple sclerosis. Brainstem atrophy is seen in chronic cases. Neurological involvements range from aseptic meningitis to vascular thrombosis such as dural sinus thrombosis and organic brain syndrome manifesting with confusion, seizures, and memory loss. Tumor necrosis factor – alpha (TNF-α) is a pleiotropic cytokine which plays a major role in the development, homeostasis, and adaptive responses of the immune system. In fact, it is central to the initiation and maintenance of inflammation in multiple autoimmune and nonautoimmune disorders. Infliximab is an IgG1 chimeric monoclonal antibody with a central human region and variable murine one. This agent binds both the soluble and the cell-bound TNF α but not TNF-β.
The blocking of TNF-α with the so-called anti TNF agents has turned into the most important tool in the management of a variety of disorders, such as rheumatoid arthritis RA, spondylo-arthropathies, inflammatory bowel disease and psoriasis. Infliximab is now widely used throughout the world for the treatment of RA and a growing list of other inflammatory arthropathies. Treatment with infliximab in RA produced a rapid and significant reduction in the number of tender and swollen joints and concentrations of serum C reactive protein (CRP). In ankylosing spondylitis, infliximab treatment was associated with significant improvement in all disease activity measures Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Bath Ankylosing Spondylitis Metrology Index (BASMI) compared with placebo. In psoriatic arthritis, treatment with infliximab was associated with improvement in both the joint and skin manifestations. The study aimed to assess the off-label use of infliximab in Behçet’s disease.

Materials and Methods

Twelve patients fulfilled the international study group for BD who were treated with infliximab at Tripoli Medical Center for more than 6 months were included in this study. Infliximab was initiated with 5mg/kg of body weight. Infusion given at (week 0, 2, 6 and every 8th week thereafter) as either first-line therapy in eight patients or given after failure of conventional immunosuppressants in the remaining four patients. All patients were assessed by clinical examination and inflammatory markers. The patients with ocular involvement were assessed clinically by an ophthalmologist every 2 months and inflammatory markers. For all patients, complete blood count, erythrocyte sedimentation rate, liver function test, hepatitis screen, urine routine examination and tuberculin test before starting infliximab were requested to monitor it’s side effect during follow up. All these investigations were normal before starting infliximab and tuberculin test was negative.

All patients consented to participate in the study. The study was done after receiving consent from the Tripoli Medical Center ethical and research committee.

Data was analyzed using SPSS computer software package. Mean and standard deviation of the age and the period of follow up were calculated. P value to measure if there is significant difference between the mean of visual acuity before starting infliximab and at the last follow up were calculated using t-test. The p value to measure if there is significant difference between using infliximab as first or second line treatment was calculated using the Z approximation test to compare two proportions.

Results

Twelve patients included in the study, the mean age was 27 years (± SD 7.8 years), ten were males and two were females. The mean duration of taking infliximab was 15.6 months (± SD 7.2 months) (Table 1). The clinical characteristics for the twelve patients are shown in Table 2.

Infliximab was started in these twelve patients for the following manifestations: In six patients the infliximab was started for ocular manifestations, two patients with neuro-Behçet’s disease, one had mucocutaneous lesions, one had vascular involvement, one with ocular and neuro-Behçet’s disease and one had ocular and vascular involvement.

Eight (67%) patients achieved remission without any relapse during the period of follow up. Two (17%) patients had only one relapse in the same organ. One had ocular attack 14 months after starting infliximab. The other patient had recurrence of oral ulcers and acnec six months after starting infliximab. In one (8%) patient, infliximab was started to treat neuro-Behçet’s manifestations. She had relapse in another organ (bilateral pulmonary embolism) and infliximab was stopped. One (8%) patient had no response; he had no change in visual acuity (only light perception in both eyes) (Figure 1).

Table 1: Demographic and clinical characteristics of the twelve patients

<table>
<thead>
<tr>
<th>Mean age at diagnosis</th>
<th>27 years ± (SD= 7.8 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male 10, Female 2</td>
</tr>
<tr>
<td>The mean duration of</td>
<td>taking infliximab 15.6 months ± (SD=7.2 months)</td>
</tr>
</tbody>
</table>

Table 2: Clinical characteristics of the twelve patients

<table>
<thead>
<tr>
<th>Clinical features of BD</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral ulcers</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Genital ulcers</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Eye lesions</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Vascular involvement</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Neurological features</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Pathergy test</td>
<td>2 (17)</td>
</tr>
</tbody>
</table>

Figure 1: The response of the twelve patients to infliximab

All patients started on oral prednisolone 60mg/day which tapered gradually to 5 mg/day.

Ten patients were on colchicin and three were on warfarin. One patient with ocular involvement was on cyclosporine and azathioprine consecutively and another one was on azathioprine only. One patient with
neuro-Behcet’s disease was on cyclophosphamide and then on azathioprine. One patient had mucocutaneous features and treated by azathioprine, methotrexate and dapsone consecutively. After starting infliximab, immunosuppressants were stopped in all patients except one and all were kept on low dose glucocorticoids (5mg/day). Eight patients with ocular involvement had bilateral ocular involvement. Changes in affected eyes included panuveitis (50%), posterior uveitis (37%), anterior uveitis (12%), vitritis (38%), retinal vasculitis (31%), vitrous degeneration (6%), cytoid macular oedema (13%) and central retinal artery occlusion (6%). None of the patients had visual acuity worsening. At the final follow-up, mean right and left eye visual acuity respectively increased from (0.23±0.33) at the baseline to (0.67±0.36) (p<0.05) and from (0.13±0.34) to (0.24±0.40) (p<0.05).

Six (75%) patients had no ocular attacks during their period of follow-up; their last ophthalmologic assessment reported no active uveitis. One (12.5%) patient at the 10th dose of infliximab had one ocular attack (bilateral active uveitis) treated by increasing the dose of prednisolone (1mg/Kg/day) and then tapered gradually, thereafter there were no more ocular attacks. One (12.5%) patient had no response. Three patients who were assessed clinically and by MRI scan had Neuro-Behçet’s Disease (NBD). MRI was done before taking infliximab and at the last visit (one year after taking infliximab). The first patient went in remission, with complete improvement of short term memory loss, left 6th cranial nerve palsy, hemiparesis and no more attacks of convulsions and complete disappearance of high signal intensity lesions in parietal area and brain stem. (Figure 2 a and b).

The second patient had significant clinical improvement with complete improvement of right side hemiparesis. But he still had emotional lability and very mild dysarthria. MRI scan showed high signal intensity lesions in frontoparietal area before starting infliximab and the presence of some residual lesions one year after. The third patient had no significant clinical improvement. She still had dysarthria and paraparesis but urine incontinence was improved, her MRI scan showed periventricular and spinal cord high signal intensity lesions before starting infliximab and no improvement occurred in the last MRI. This patient had bilateral pulmonary embolism one year after starting infliximab and it was stopped. There were two patients with vascular involvement. One patient had recurrent left femoral vein thrombosis. At two months follow up, the ESR was decreased from 52 mm/hr to 12 mm/hr. Doppler ultrasound of left lower limb showed patent deep venous system. The other patient had also left femoral vein thrombosis. During follow up the ESR decreased from 30 mm/hr to 5 mm/hr. Doppler ultrasound showed normal left femoral vein. In one patient the infliximab was started because he had refractory mucocutaneous features which manifested by recurrent erythema nodosum on legs and forearms, recurrent oral ulcers and recurrent pustules over the chest. This patient was on methotrexate, azathioprine, colchicine and dapsone which were used consecutively and didn’t show any improvement. The patient from the 2nd dose to the 6 dose was in remission. Then he developed a relapse in term of pustules on chest and oral ulcers, for that we planned to increase the frequency of

**Figure 2-a:** MRI brain showed area of high signal intensity before infliximab (Arrow)

**Figure 2-b:** MRI brain showed disappearance of high signal intensity area after infliximab (Arrow)
infliximab every 6th week instead of 8 weeks and he went in remission thereafter. No drug side effect occurred in these twelve patients.

Discussion

In eight patients who started on infliximab as first line therapy, the remission occurred in 6 (75%) patients while in the other four who were taking infliximab after failure of conventional immunosuppressants, the remission occurred in two (50%). The p-value was 0.20 which is not statistically significant. There was no statistically significant difference between using infliximab as first or second line treatment in our patients and this was because of small number of patients in our study. For comparison we recommend to do large randomised controlled studies to decide either to use it as first or second line treatment.

In a multicenter study of infliximab for refractory uveoretinitis in Behcet’s’ disease done in Japan by Okada et al14, the efficacy of infliximab was analyzed in 50 patients. The mean best-corrected visual acuity improved from 0.736 at the first infliximab infusion to 0.616 at the end of one year (p=0.01). They concluded that, at the end of one year, uveoretinitis had improved or improved some what in 92% of patients, accompanied by improvement in the mean visual acuity. Another study by Adler et al2 which included seven cases with vascular involvement concluded that, there is a striking effect of infliximab in severe vascular BD. They confirmed the fact that surgery of inflamed blood vessels should be avoided, that no foreign material such as stents should be used during active inflammation, and that disease remission should be achieved before surgery is performed. Still there are no large studies on infliximab treatment in Neuro-Behçet’s Disease NBD. Zeydan et al15 reported 11 patients with NBD treated with infliximab in their inpatient clinic. Four patients showed clinically significant improvement and seven patients were in remission. In our study, we had three patients, one was in remission, one showed significant clinical improvement and one had no response. The finding of our small cohort should be confirmed using a standard controlled trial.

Conclusion

Infliximab is effective in inducing remission of BD. The good effect together with excellent tolerability suggests that infliximab can be used as first line drug in BD.

Acknowledgment

To Yosif Mohamed Emhemmed, Head of Statistics Department, Faculty of Science, Tripoli, Libya.

References

Reversible blindness in a patient with systemic lupus erythematosus: case report

Ochieng PO, Bandagi SS

Abstract

Neuropsychiatric manifestations can occur in majority of patients with Systemic Lupus Erythematosus (SLE). We describe a patient who presented with acute onset binocular visual loss and was found to have inflammation of optic chiasma on imaging. The patient was treated with immunosuppression. She responded favorably and had complete visual recovery. We concluded that prompt management of atypical presentation of SLE can have enormous positive effect on outcome and quality of life.

Introduction

Systemic Lupus Erythematosus (SLE) is a multisystem disorder with multiple neuropsychiatric manifestations. Neuropsychiatric manifestations of SLE are common. We present a rare case of SLE with isolated optic chiasmitis presenting with near total blindness that was reversed with treatment.

Case report

A forty eight year old black female with past medical history of remote pulmonary embolism and a ten year history of SLE presented with rapidly progressing loss of vision. She described acute onset blurring of vision affecting her peripheral vision with initial central sparing that ended in near complete bilateral loss of vision within two weeks. She reported no eye injury or pain, fever, headache, vomiting, weakness or numbness. She reported no rash, arthralgia, joint swelling or any other symptom. She had no similar symptoms in the past. Her only medication was hydroxychloroquine at a dose of 200 mg every 12 hours which she had taken for 8 years for SLE. She was a non-smoker and did not take alcohol or use drugs. She had one spontaneous abortion at gestational age of 8 weeks as her first conception followed by four full-term pregnancies with the last delivery at the age of 36.

On examination she was a well nourished female and was in no distress at rest. Her vital signs were within normal limits. Eye exam revealed visual acuity of 14/200 on the right and perception of light on the left with visual field and color perception testing was limited due to reduced visual acuity. The rest of the eye examination including fundoscopy was normal. Her systemic examination including the rest of neurological examination was within normal limits.

Hemogram revealed thrombocytopenia of 89,000/microLitre, hemoglobin of 12.2 g/dl and normal leucocyte count. CRP was elevated at 0.14 mg/dl (ref 0-0.8), Antinuclear Antibody (ANA) and anti-double stranded-DNA were positive at titers of 1:160 and 1:160 respectively with homogenous pattern of ANA. Anti-Ro was positive and Anti-La was negative. Her electrolytes, urea, creatinine and hepatic panel were unremarkable. Urinalysis was unremarkable. Lyme titer was negative. Anti-phospholipids, beta-2 glycoprotein and Anti-Neuromyelitis Optica (NMO) antibody were negative. Brain MRI revealed thickening, edema, and enhancement of the optic chiasm consistent with optic chiasmitis (Figure 1). Lumbar puncture results were normal with normal protein, no cells and negative for oligoclonal bands.

The hydroxychloroquine was discontinued at admission with initial concern for hydroxychloroquine toxicity. She was subsequently treated with intravenous pulse methyl prednisolone for 3 days followed by oral prednisone of 60 mg daily. She had gradual improvement of vision with full restoration of vision to visual acuity of 20/20 on both eyes in 6 weeks. Follow-up MRI was normal. The prednisone was tapered off gradually after 8 weeks and her vision remained normal on subsequent follow-up for over 1 year.
Figure 1: Pretreatment MRI of the brain (left- normal size T1 image, middle- T1 image zooming on the optic chiasma and right- T2 image zooming on the optic chiasma)

Discussion

This patient fulfilled at least four out of the eleven components of the diagnostic criteria for SLE with positive ANA, positive anti-double stranded DNA antibody, neurological manifestations and thrombocytopenia. There are at least 19 neuropsychiatric manifestations of SLE and they occur in up to 90% of SLE patients. Most visual complaints from SLE result from retinopathy and anterior uveitis. Optic chiasma involvement has however been rarely documented. As in our case it is even more rare to have isolated optic nerve or optic chiasma involvement without other clinical manifestations. The leading differential diagnosis that was considered included glioma, granulomatous diseases like sarcoidosis and tuberculosis and lymphoma. Hydroxychloroquine eye toxicity as a possible cause of blindness prompted discontinuation of the medication although this was unlikely considering the absence of the pathognomonic corneal keratopathy characterized by whorl-like corneal epithelial deposits and maculopathy with “bull’s eye” lesion or atrophy of the retinal pigment epithelium. Another plausible differential diagnosis was neuromyelitis optica but this was considered less likely after the positive SLE markers and negative anti-NMO antibodies. A differential diagnosis for reversible blindness whose criteria this patient did not fulfill is posterior reversible leukoencephalopathy. This is a clinicoradiologic entity characterized by altered mental status, seizures and visual deficits associated with reversible changes on Magnetic Resonance Imaging (MRI) of the brain.

The pathophysiology of SLE optic chiasmitis remains an area of postulation and may involve auto-antibodies and immune dysregulation, vasculitis, non-inflammatory vasculopathy and thrombosis. The inflammatory and immune pathogenesis is supported by response to immunosuppressants.

High dose steroid is the appropriate therapy for this sight threatening condition and the response is usually good if treated early. There have been few published case reports where alternative treatments like IV cyclophosphamide and methotrexate have been tried. Hydroxychloroquine does not seem to have protective effect against this condition as observed both in our case and in the case reported by Frohman et al.

Conclusion

SLE remains a great medical masquerader and clinical vigilance is necessary in atypical presentations. Prompt therapy, therefore, can make an enormous quality of life difference in extreme presentations of SLE.

References

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3. Case reports should have a background, introduction followed by the discussion with not more than 20 references. The word count should not exceed 2000 words. Perspectives or scientific letters should be in prose form and should not exceed 1500 words.

4. References should be numbered in order of appearance (Vancouver style) and only those cited should appear in the reference list.
Afr J Rheumatol 2012; 1(1): 8-12

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