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Early arthritis management in Africa: moving on to a reality

Moots RJ¹, Mwachai SD²

Rheumatoid arthritis is associated with considerable morbidity and disability in African patients as well as the rest of the world¹. In western countries, even though there is provision for considerable patient support, studies have shown that almost a third of patients who were gainfully employed at disease onset have to retire due to the disease within five years². The situation in Africa, where there is less resources for health care, is likely to be even worse. In Britain, work disability at five years is observed more in patients who are manual labourers and/or with a high baseline HAQ². Although it has been suggested that RA in Africa is of a mild phenotype, some studies report a high mean HAQ, probably reflecting high disease activity. In the African continent, where a large proportion of the labour force occupies manual positions and where the vast majority of patients have high HAQ scores, it is imperative that African rheumatologists develop measures to facilitate the early diagnosis of rheumatoid arthritis and improve the devastating disease outcomes that occur at present³.

The approach to managing RA worldwide has changed dramatically over the years, to emphasize early diagnosis and treatment, which is associated with enhanced outcomes. There is accruing evidence to suggest that the optimal time to intervene therapeutically and improve outcomes lies within three months from symptom onset, which may only be vague symptoms such as fatigue³⁴. With prolonged delays in diagnosis in African countries, high morbidity and disability are sadly to be expected¹.

Early diagnosis of RA is now possible with highly sensitive imaging, such as ultrasound and MRI⁵. Many African tertiary centres may be equipped with some of this equipment, yet lack staff familiar with musculoskeletal techniques. The inadequate provision of rheumatologists in tertiary centres is long standing and the gap in service provision too large to fill as fast as we would wish. There is also a huge need in Africa to understand musculoskeletal diseases in the community and at basic hospital levels. Identifying MSK diseases at the community level, with appropriate simple treatment and referral on, when required, is a paramount issue. Unless clear referral systems, involving the community, are established, with specific emphasis on screening, early diagnosis will remain elusive.

We believe that treatment should not be delayed because of lack of access to imaging, even simple radiography, especially in the setting of persistent symptoms. We recommend that GALS, a validated screening tool for MSK disease, is taught and rolled out widely to community health workers, to expedite early identification of patients with these problems⁶. It may also be practical to educate the community workers on how to cautiously begin steroids, as temporary bridging therapy, under appropriate supervision.

Whilst therapeutic options for RA have evolved tremendously, with biologic therapies further enhancing outcomes, these agents will be unaffordable for most African patients, even as the biosimilars emerge, for the foreseeable future. However, if African countries focus on early diagnosis and an expedited referral system, the continent may still achieve good outcomes. Targeted early therapies using low cost DMARDs such as methotrexate are the type of strategies that will benefit the African continent most. Following up rheumatoid patients with CDAI assessments in a targeted approach has been shown to be a simpler and more cost effective in this setting⁸. Even though some of the studies may have been underpowered, treat to target strategies in early arthritis that utilised DMARDs, plus or minus systemic glucocorticoids, have been very successful in inducing remission in a large percentage of patients within two to five years⁹-¹¹, even suggesting a suppression in MRI inflammation and prevention of structural damage in some cases. These encouraging studies suggest that only a minority of patients with an early diagnosis will not respond to a treat to target strategy, with remission occurring in a large proportion. Other lifestyle factors that may influence outcome, including obesity and smoking, should also be addressed by the attending rheumatologists and appropriate actions implemented¹².

Finally, much remains to be learnt about the different genetic variants

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associated with RA in African populations, building on the work of Govind and colleagues in South Africa. We strongly urge researchers to replicate such studies in other African regions, to help identify genetic loci that confer increased risk of RA in the diverse population groups present in Africa. Prognostic markers need to be clearly identified and long term outcome studies are required. It is also time to try the different therapies in our population, to clearly understand our pharmacokinetics and pharmacodynamics to the different drugs used in rheumatoid arthritis. As better systems for the care of rheumatic diseases develop, more rheumatologists are trained in Africa and education about rheumatic diseases occur in African medical schools and to community doctors, we strongly believe that the time has come for African rheumatology to begin to grow and flourish.

References

Clinical utility of autoantibodies and biologic markers in rheumatoid arthritis

Genga EK, Adam Sheik M, Oyoo GO

Abstract

Objective: To review the current and emerging autoantibodies and biologic markers in rheumatoid arthritis.

Data source: Published original research work and reviews were searched in English related to pathophysiology, diagnosis and auto antibodies in rheumatoid arthritis.

Study design: Only articles that emphasize on auto antibodies.

Data extraction: Online and library searches done.

Data synthesis: Data added and summarized.

Conclusion: There is an emerging role of biomarkers as efficient diagnostic and prognostic markers of immunopathogenicity of rheumatoid arthritis. Early identification of patients with Rheumatoid Arthritis (RA) and, in particular, those likely to assume a more rapidly destructive form of disease, is important because of the possible benefit from early, aggressive intervention with modifying agents. This realization has prompted the investigation and measurement of numerous biologic ‘markers’ in blood and markers under consideration are accessible in routine practice, many are in the stage of experimental evaluation and require access to specialized technology and customized reagents. A biomarker can be defined as a measurable indicator of either normal or pathogenic processes or pharmacological responses to therapeutic interventions. Clinically, biomarkers are commonly used for diagnostic (disease identification) and prognostic (predicted outcome or progression) purposes.

Diagnosis biomarkers distinguish individuals with active disease from healthy individuals. Prognostic biomarkers stratify patients according to prognosis. In RA, they identify patients at risk for rapid disease progression or early radiologic damage. Prognostic biomarkers are present at disease onset and do not change with treatment. Biomarkers of treatment response detect early and subtle changes in disease activity and are modifiable by effective treatment. Biomarker levels should be very sensitive to spontaneous or treatment-induced changes in disease activity, increasing in response to a disease and decreasing in response to effective treatment.
Table 1: Summary of the biomarkers/antibodies and their role in rheumatoid arthritis

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<th>Biomarker/ Antibody</th>
<th>Role in rheumatoid arthritis</th>
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<td>Diagnosis, staging, prognosis</td>
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<td>Erythrocyte sedimentation rate</td>
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</tr>
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What makes biomarkers so hard to identify?

Dozens of potential biomarkers have been identified in RA, yet few are ready for clinical use. The potential reasons include the following:

(i) Genetic variations may alter the pathogenic activity of certain biomarkers, causing small concentrations to be highly pathogenic in some patients and large concentrations to be relatively benign in others, thereby clouding our ability to interpret them.

(ii) RA is a highly heterogeneous disease, and some biomarkers may play a more pathologically-dominant role in certain patients than in others. Different biomarkers are also associated with different pathologic mechanisms (e.g. inflammation vs. cartilage degradation). This may be predominant at different stages of disease progression.

(iii) Biomarker levels in blood and other body fluids may not reflect levels in the microenvironment of the joint. The rate at which various molecules (e.g., TNF, IL-6) leak from within the joint to systemic body fluids may vary between patients, or even from joint to joint within the same patient. While many biomarkers are active in joint destruction or other pathological mechanisms, the concentrations of some biomarkers may not reflect the degree of their contribution.

This topic will review those markers that are used in clinical practice as aides in the diagnosis of RA or for prognostic purpose in patients with already established disease. Other tests that are still investigational or are of historic interest are also discussed.

Diagnostic, staging and prognostication biomarkers

Among the many biologic markers that have assessed for usefulness in estimating disease activity and prognosis of rheumatoid arthritis, only a few have found a role in clinical practice. At present, the main clinically useful biologic markers in patients with RA are rheumatoid factors and antibodies to citrullinated peptides for both diagnosis and predication of prognosis.

Rheumatoid factor

Rheumatoid Factors (RF) are autoantibodies directed against the FC portion of IgG. They are found in 75 to 80% of RA patients at some time during the course of their disease. As with any diagnostic test, however, the predictive value is also affected by the estimated likelihood of disease prior to ordering the test (ie, the pre-test probability). RF has a low positive predictive value if the test is ordered among patients with a low prevalence of RF-associated rheumatic disease or with few clinical features of systemic rheumatic disease. In a study of consecutive tests ordered by healthcare providers in a large academic medical center in the US, the prevalence of RA was approximately 13%. The positive predictive value of RF (the likelihood of having disease if the...
RF is positive) was only 24% for RA and 34% for any rheumatic disease. Thus, RF has a low positive predictive value if the test is ordered among patients with a low prevalence of RF-associated rheumatic disease or with few clinical features of systemic rheumatic disease. RF production may also occur in other diseases for example, some connective tissue diseases, such as Systemic Lupus Erythematosus (SLE) and primary Sjogren’s syndrome. In addition, RF levels may be elevated in patients with malignancies (multiple myeloma) and certain infections such as HIV, malaria, rubella, hepatitis C, and following vaccinations.

Rheumatoid factor may have some prognostic value with regard to disease manifestations and activity. RF positive RA is associated with more aggressive joints disease, and is more commonly complicated by extra articular manifestations than sero-negative RA5. Studies have shown that rheumatoid nodules and vasculitis occur almost exclusively in seropositive patients and these findings are associated with increased mortality6. A case control study of 135 women with early RA found that patients with persistently positive RF had more erosions, nodules, extra articular disease and functional disability. They also noted that it was also associated with rapid radiographic progression and disease activity than sero-negative, or intermittently sero-negative individuals over a mean period of six years of follow up7.

It has been noted that the presence of RF may antedate the clinical development of RA8. Population-based studies have shown that some healthy people with a positive Rheumatoid Factor (RF) develop RA over time, especially if more than one isotope is persistently elevated and if patients have high levels of RF9, 10. Retrospective study of stored blood samples collected as part of routine blood donation has demonstrated that nearly 30% of those who later develop RA have serum RF present for a year or more prior to diagnosis11.

A Finish study of cohort of healthy individuals found that 9 of 129 subjects with positive sensitized sheep red blood cell agglutinations tests for rheumatoid factor subsequently developed seropositive RA over a 10 year investigation period, as compared to only 12 of 7000 subjects with negative test6. Thus, the presence of a positive sensitized sheep red blood cell agglutination test in a healthy individual is associated with a relative risk of approximately 40 for the development of RA. In the same study, however, 120 of 129 patients with positive RF did not develop RA over the 10 year period, demonstrating the lack of predictive value of the test.

**Anti-Cyclic Citrullinated Peptide (CCP) antibodies**

ELISA assays based upon either filaggrin derived from human skin or synthetic citrullinated peptides have high specificity and sensitivity for RA12. The target amino acid in filaggrin is citrulline, a post-translationally modified arginine residue. An ELISA assay that detects antibodies of cyclic citrullinated peptides. It has been reported to have a sensitivity and specificity of 47 to 76 and 90 to 96% for RA, respectively13. The sensitivity and specificity of anti-CCP antibodies for RA is dependent on the characteristics of the assay kit employed. The positive and negative values depend on both the assay and the study population. Higher values are reported with a later generations assay than with the origin14. What is the level of anti-CCP antibodies in normal people? They have been tested in ethnically diverse RA cohorts from North America, Europe, and Asia, and rates of anti-CCP detection are remarkably consistent. These studies used different controls, including healthy individuals and populations of various arthritic and non-arthritic inflammatory diseases.

The data has consistently shown that no control population has an equivalent rate of anti-CCP positivity to that found in RA, and the specificity remains high. This is despite having used controls with similar inflammatory disease processes. Early in the disease process, RA is often difficult to distinguish from other types of inflammatory arthritis and systemic inflammatory conditions, as their initial presentations may be similar. Several studies have examined the utility of anti-CCP antibody testing in distinguishing RA from other inflammatory diseases, by studying cohorts of patients who presented with non-specific early inflammatory arthritis. The ELISA for anti-CCP may be useful in the differential diagnosis of early polyarthritis. This was shown in a study on early arthritis study where 318 patients with undifferentiated inflammatory arthritis of less than 2 years duration were followed for 3 years14. Diagnosis of rheumatoid arthritis was made in 93% of those with an initial positive anti-CCP2 antibody test. In this study, anti-CCP antibodies conferred an odds ratio of 38.6 for the diagnosis of RA, compared to an odds ratio of 9.8 for rheumatoid factor.

A similar study on 524 patients with early undifferentiated arthritis of less than 2 years duration had anti-CCP antibody testing at inception. They were followed up longitudinally for 2 years15. After 2 years, 60% had self-limited inflammatory arthritis, 16% had persistent non-erosive arthritis, and 24% had persistent erosive arthritis. Anti-CCP positivity conferred an odds ratio of 4.58 for persistent vs. self-limited arthritis, as well as an odds ratio of 4.58 for erosive vs. non-erosive disease. Rheumatoid factor conferred an odds ratio of 2.99 for persistent vs. self-limited arthritis, and an odds ratio of 2.99 for erosive vs. non-erosive disease. Among patients with early oligo-or polyarthritis, anti-CCP testing appears to be predictive value in the 1gM-RF negative subgroup. This was illustrated by a prospective study that included 178 such patients16 where they found that radiographic progression (More than 5 units by sharp score) was more frequent in the anti-CCP positive patient than those with negative test results (40 versus 5%, negative predictive value 95%). The anti-CCP test correctly predicted whether or not there would be worsening radiographic damage in 83% of these 1gM-RF negative patients. These findings were supported by similar data in studies of 282, 454 and 182 subjects16.

Combination of anti-CCP antibodies and 1gM RF may be better for excluding the diagnosis of RA than
by testing for either antibody alone. Findings in respect to test performance from a study comparing the results of serologic testing in 196 patients with a clinical diagnosis of RA and 239 controls were anti-CCP-sensitivity 56%, specificity 90%, IgM RF – sensitivity 73 and specificity 82% and IgM RF and anti-CCP – sensitivity 48 and specificity 96%. Patients with RA show considerable variability in disease activity, which can be difficult to predict at the onset of disease. Anti-CCP antibodies have proven useful in identifying those patients who are likely to have clinically significant disease activity. Some reports describe a decrease in titre of anti-CCP antibodies following successful treatment of RA. In a RA treatment trial, 35% of patients had a decrease in anti-CCP2 titres of 415%, while 19% had an increase of 415%; 46% of patients had anti-CCP2 titres within 15% of the baseline values. All but 5 of 242 patients with a positive anti-CCP2 antibody test remained positive when tested serially over a 3-year period. In a similar study, serial anti-CCP2 levels were measured in 43 patients with RA who were treated for at least 2 years. Mean anti-CCP2 titres at inception were 107.9.5 U, which fell to a mean of 92.9.8U (p=0.0001) after 24 months of treatment. Titres were more likely to decrease in patients showing a greater degree of clinical improvement.

In addition to disease activity, irreversible damage from RA is an important outcome with significant impact on quality of life and functional capability. Predicting which patients will accrue damage is difficult, and disease activity parameters are not always accurate in predicting subsequent joint destruction. Anti-CCP antibody positive patients with early RA may be at increased risk of progressive joints damage. This was illustrated in a study of 145 such patients among whom there was more radiographically apparent damage after five years of observation in those with detectable anti-CCP antibodies than among the RF-positive patients. The presence of anti-CCP antibodies was also predictive of more rapid radiographic progression in patients with early RA. In a study addressing the progression of radiological damage in RA, anti-CCP1 antibodies were measured in 273 RA patients with <1 year of symptoms. The patients were followed for at least 6 years and had plain radiographs of the hands and feet performed every 6 months. X-rays were graded by a radiologist blinded to the clinical data. After 6 years, anti-CCP1 positive patients had significantly more radiographic damage than anti-CCP1 negative patients (p < 0.05).

What is the role of anti-CCP antibody screening in rheumatoid arthritis? Ideally, screening healthy individuals at high risk of developing RA, for example those with a family history of RA, could allow for increased vigilance and the possibility of early intervention. As with RF, anti-CCP antibodies may be present prior to the appearance of symptoms of RA as shown in a case-control study of 79 patients with RA who had stored serum available from blood donations prior to the development of RA (1 to 51 samples per patient, dating up to 14.5 years prior onset of RA) had detectable anti-CCP and/or anti-IgM RF on at least one occasion and 41% had anti-CCP detectable when symptoms first develop.

In another study of 59 patients with RA who had donated blood prior to the onset of disease, stored serum was analyzed for the presence of RF, anti-CCP, and for the HLA shared epitope. Of these three markers, anti-CCP was associated with the greatest risk of development of RA (odds ratio (OR) of 16, while IgA RF and presence of the shared epitope were less powerful predictors (OR of 6.8 and 2.35, respectively). The combination of one or more HLA alleles for the shared epitope and anti-CCP antibodies was highly predictive of the subsequent development of RA; with an Odds ratio of 67. Anti-CCP antibodies can appear years in advance of actual disease, and may eventually allow for identification of individuals who are likely to develop disease.

Erythrocyte sedimentation rate

The Erythrocyte Sedimentation Rate (ESR) determination is a simple and inexpensive laboratory test that is frequently ordered in clinical medicine. The test measures the distance that erythrocytes have fallen after one hour in a vertical column of anticoagulated blood under the influence of gravity. The rate at which erythrocyte fall through plasma, the ESR, depends largely upon the plasma concentration of fibrinogen. ESR can be greatly influenced by the size, shape and number of red cells, as well as by other plasma constituents such as immunoglobulin. Thus, results may be imprecise and sometimes misleading.

Despite the shortcoming, an elevated ESR in patients with early RA is predictive of greater radiographic joint damage in subsequent years despite treatment with conventional disease modifying anti-rheumatic drugs. ESR values tends to correlate with disease activity in rheumatoid arthritis and may be useful for monitoring therapeutic response. ESR can aid in the diagnosis of RA, but it cannot be used solely for diagnosing RA. It is very useful when used with other parameters as outlined in the American College of Rheumatology guidelines, in the diagnosis and follow-up of RA patients. Wolfe and Micahd showed that the ESR can be elevated when RA is quiescent clinically and vice versa. The authors concluded that the ESR role in the diagnosis and follow-up of RA patients may not be accurate.

C-reactive protein

C-reactive protein (CRP) has been advocated as an objective measure of disease activity in RA. Unlike the ESR, CRP can be measured using stored serum samples, is independent of the haemoglobin concentration, and can be performed in automated serum analyzer. Radiologic damage, as assessed by erosion counts in RA, is significantly more likely to progress when CRP and ESR are elevated, irrespective of the presence or absence of RF, and irrespective of therapeutic intervention.

Elevation of both ESR and CRP together are stronger indicators of radiologic progression than CRP alone. In one study of 147 patients, for example,
absence or progression of radiologic joint damage after two years was correctly predicted in 83% of the patients using a combination of disease activity at presentation, (assessed by ESR, CRP or disease activity score) DR status and RF positivity27.

However, a wide variation in the relationship between the degree of radiographic change and cumulative CRP was noted between patients, particularly those with low CRP levels. This inter-individual variability could not be accounted for by HLA DR4, positive RF, sex, or age and limits the value of serial measurement of acute phase protein in predicting radiologic progression.

Investigational bio-markers for disease severity

Proinflammatory cytokines

Pro inflammatory cytokines such as Tumour Necrosis Factor (TNF), interleukin 1 (IL-1), and IL-6 have been studied as surrogate markers for disease activity and inflammation in RA28. In early RA, a characteristic mix of cells and cytokines work together within the inflamed synovium to degrade cartilage and bone. Over time, this destructive activity typically manifests as RA. Ideally, it would be beneficial for rheumatologists to detect wayward cells and cytokines in patients with subclinical RA prior to symptom onset, or even in those who are only at risk for developing the disease29. The challenge is discerning a clinically relevant signal from biological background noise associated with normal physiological variations in cytokine levels. Inflamed synovium is thought to be the principal source of plasma IL-6 in RA, since IL-6 is often detected in high concentration in the synovial fluid. Thus, it has been postulated that plasma IL-6 concentration might reflect joint inflammation better than acute phase protein levels. A major stumbling block with Interleukin -6 (IL-6) is that it lacks specificity because it also has a major stimulatory effect on hepatic synthesis of acute phase protein. For example, serum IL-6 levels can vary up to 100-fold between individuals, increase with physical exertion, and change depending upon the time of day29. There is evidence to support its regulatory role in platelets production and etiopathologic role in the anaemia of chronic disease.

Inflammatory cells

Researchers have studied various synovial cell populations harvested from joint biopsies in an effort to detect potential biomarkers of early joint damage. Within the heterogeneous cellular infiltrate, promising biomarkers include macrophages, T cell infiltrates, and lymphoid cells32. A promising marker of disease activity appears to be a certain type of macrophage—Sublining CD68+ macrophages that decreases in number in response to RA treatment33. Other potential synovial biomarkers have yet to be validated as biomarkers in RA. However the major stumbling block about these markers is how they can be tested on reliability and consistency. Even if more reliable markers are identified within the synovium, arthroscopic biopsies are regarded as an invasive technique and are unlikely to be used regularly in clinical practice28.

Markers of joint damage or destruction

Although inflammatory markers provide important diagnostic and prognostic information in RA, they lack specificity to RA disease activity. For monitoring disease activity in rheumatoid arthritis biomarkers that reflect turnover in the synovium, cartilage, and bone may be more useful. Candidate biomarkers include matrix metalloproteinases (MMP), which are enzymes involved in articular cartilage degradation; urinary carboxyterminal crosslinking telopeptides of type I (CTX-I) and type II (CTX-II) collagen levels, which are markers of collagen breakdown; and receptor activator for nuclear factor B ligand (RANKL), a marker of bone degradation28.

As part of the SPECTRA phase II clinical trial, researchers evaluated a panel of 22 biomarkers as potential indicators of disease activity, treatment response, and radiographic progression48. Among the markers of joint damage, matrix metalloproteinase 1 (MMP-1), MMP-3, and tissue inhibitor of metalloproteinase 1 (TIMP-1) showed the most promise. Both MMP-1 and TIMP-1 were significantly associated with radiographic progression, and early TIMP-1 activity following treatment onset predicted later therapeutic outcome35.

Matrix metalloproteinase can degrade collagen and contribute to cartilage and bone destruction in RA. Genetics has been shown to play a major role as carriage of a polymorphism in the promoter region of the gene for matrix metalloproteinase 3 (MMP3) may be associated with more severe disease. This was illustrated in one study of 102 patients with early RA37. Homozygous carriage of particular polymorphism in the promoter region of the MMP3 gene (6A/6A) was associated with the presence of more progression of joint erosion and joint space narrowing than carriage of one or more alleles of a different type (5A).

The synovium is thought to be a dominant source hyaluronan, a marker that is strikingly elevated in the serum of patients with RA. In vitro studies demonstrates that synovial lining cell of rheumatoid joints produce detectable amount of hyaluronan, while lining cells on normal joints do not. Despite a short half-life of lining cells of 15 minutes, serum hyaluronan concentration has been found to correlate with disease activity38. One prospective study has suggested that, in early RA, serum hyaluronan may reflect ongoing joint destruction, and may even predict subsequent joint damage39. However, elevated serum levels of hyaluronan can be non-specific since they may vary with physical activity independent of the degree of synovitis.

Other markers that may be predominantly released from the synovium are matrix metalloproteinase 1 and 3 (MMP-1 and MMP-3), enzymes that fragment matrix collagen. Elevated levels of MMP-3 and/or MMP-1 may correlate with increased radiographic joint damage40.

Markers of cartilage metabolism may have some prognostic value in patients with RA. In early RA it has been shown that high serum level of cartilage oligometric
matrix protein (COMP), a member of the thrombospondin protein family can predict severe disease characterized by subsequent large and small joint destruction. The same study that measured serum level of COMP in patients with RA, also measured serum levels of a putative markers of cartilage aggrecan synthesis, epitope 846, located on the chondroitin sulphate rich area of the aggrecan molecule. The epitope 846 levels were found to be elevated only in a group of patients with slow joint destruction, as compared with a group matched for age, gender and disease duration but with more destructive joint disease. These data indicate the presence of cartilage reparative processes in the group with a more benign course, and suggest that elevated 846 epitope is indicative of a more favorable prognosis.

The aggrecan content of synovial fluid may also predict joint destruction. The chondroitin sulphate rich region of aggrecan is most abundantly detected in synovial fluids recovered from joints with little radiologic evidence of destruction, whereas the hyaluronan binding region of core protein is released in more severely damaged joints. Measurement of cross-linked C-terminal peptides from type II collagen (CTX-II) in urine provide some prognostic information. A correlation between the excretion of these peptides and radiographic progression up to five-years in patients with early RA has been noted. Similarly, urinary excretion of peptide derived from the helical portion of type 2 collagen (HELIX-II), also correlates with radiographic progression and is independent of other variables, including baseline CRP levels, joint damage, and urinary CTX-II excretion. Findings of a study on rheumatoid arthritis patients revealed increased levels of both HELIX-II and CTX-II correlated with the highest risk of radiographic progression compared to those without an elevation of either of these markers.

As with cartilage, several bone specific markers are available and may have a useful purpose in patients with RA. Bone degradation can be assessed by detection of pyridinoline cross-links in urine. The pyridinoline levels have been found to correlate with disease activity in RA and diminishes after treatment with pulsed glucocorticoids and DMARDS.

Immunoassays are now available for measurement of other serum markers for bone collagen degradation like carboxyterminal telopeptide of type I collagen (ICTP). A three year follow up study in RA patients found elevated levels of serum ICTP compared to healthy controls. Throughout the follow-up, serum ICTP levels correlated with inflammatory parameters, and from the first year on, with the radiologic changes assessed annually. Initial ICTP levels correlated better than the other variables of disease activity with the subsequent erosive progression of joints, suggesting that its measurement may serve as a prognostic marker for joint damage in early RA. A subsequent study found that ICTP levels in synovial fluid correlated better with prognosis than serum levels. Bone sialoprotein is an osteoblast-derived protein preferentially expressed in juxtaarticular bone. Bone sialoprotein levels in synovial fluid correlate with joint destruction in both RA and osteoarthritis.

**Investigational markers for treatment monitoring**

Given the complications of the disease, high costs and potential safety risks associated with multiple courses of ineffective therapy, it would be highly preferable to be able to refer to a treatment algorithm that uses biomarkers of treatment response to assign patients to the type of therapy most likely to promote early disease control. The identification of biomarkers that would predict disease response would have an enormous impact on outcome. Unfortunately, research on predictors of treatment response in RA is still young so any major breakthroughs appears to be well down the road. We discuss some bio markers that have shown promise for treatment monitoring.

**Bio-markers to methotrexate therapy**

Treatment of newly-diagnosed RA often begins with methotrexate (MTX), followed by the switch to or addition of another DMARD or biologic agent in those who fail MTX monotherapy. As patients progress through treatment options, many will try multiple agents before finding the right combination that adequately controls their RA. Approximately 30% of patients with RA who begin MTX treatment discontinue its use within 2 years due to side effects or lack of efficacy. As a prodrug, MTX requires enzymatic conversion to MTX polyglutamates (MTXPGs) to exert anti-inflammatory activity within the joints. However, several Single Nucleotide Polymorphisms (SNP) involved in MTX absorption and metabolism have the potential to interfere with the therapeutic effect of MTX. One commercially-available assay measures MTXPG metabolites to determine whether partial or non-responders to MTX might benefit from continued dose escalation or require a change in therapy.

**Role of genetic factors in monitoring treatment**

Five anti-TNF agents are currently available for the treatment of RA— infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol. Large-scale studies evaluating treatment response to TNF inhibition are only available for infliximab, adalimumab, and etanercept. Although the therapeutic utility of TNF blockade is well established, approximately one-third of patients with RA have minimal or no response to anti-TNF therapy. Potential markers of treatment response may include single nucleotide polymorphisms in genes known to be involved in RA pathogenesis, genes encoding TNF receptors, or genes implicated in TNF metabolism. The −308G A/G polymorphism has emerged as a significant predictor of response to anti-TNF treatment. In a meta-analysis of 311 patients with RA, those who carried the A allele had a poorer response to anti-TNF therapy than those with the G allele. In a study of patients treated with infliximab, those with the GG genotype were twice
as likely to respond to treatment as those with the AG or AA genotype. The predictive value of the −308G/A/G polymorphism has also been validated in trials of etanercept and adalimumab.

Approximately one-third of patients do not respond to treatment with tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody, suggesting the presence of a distinct subset of nonresponders. SNPs for IL-6 influence the amount of IL-6 produced in response to various conditions and may influence the potential for response to anti-IL-6 therapy. For example, the −174 C/G polymorphism of the IL-6 gene significantly influences the amount of IL-6 produced in response to IL-1 and other inflammatory stimuli. The C allele, which is present in approximately 40% of individuals, is associated with significantly lower levels of plasma IL-6. In patients with unusually low IL-6 concentrations, an IL-6 inhibitor may have little therapeutic benefit. An assay for the −174 C/G polymorphism may help to identify candidates who are more likely to benefit from anti-IL-6 therapy.

**Conclusion**

This paper outlines the auto antibodies and biologic markers used in the diagnosis and management of rheumatoid arthritis. There is an emerging role of biomarkers as efficient diagnostic and prognostic markers of immunopathogenicity of rheumatoid arthritis. They have been incorporated into various rheumatoid arthritis diagnostic and prognostic tools. These include DAS, ACR, EULAR, Simplified (SDAI) or Clinical (CDAI) Disease Activity Index criteria to assess disease activity and therefore treatment outcomes. Each method involves all or a combination of joint evaluation to varying degrees, and laboratory analysis of acute phase proteins such as Erythrocyte Sedimentation Rate (ESR) or C-reactive protein (CRP), and patient/physician subjective measures for disease activity or pain. This offers clinicians potentially reliable and objective tools in monitoring treatment of these patients. Early identification of patients with Rheumatoid Arthritis (RA) and, in particular, of those likely to assume a more rapidly destructive form of disease is important because of the possible benefit from early, aggressive intervention with disease-modifying agents. This realization has prompted the investigation and measurement of numerous biologic “markers” in blood and joint fluids, which may serve as indicators of progression and the response to therapy. Although some of the markers under consideration are accessible in routine practice, many are in the stage of experimental evaluation and require access to specialized technology and customized reagents. Increasing our understanding of molecular triggers and targets driving pathogenesis of rheumatoid arthritis is crucial. This will lead to development of a signature biomarker that can predict persons at risk of developing rheumatoid arthritis, RA patients are predisposed to joint damage and predicting therapy response. This will offer rheumatoid arthritis patients with a more personalized tailor medicine to improve diagnosis, treatment and disease outcomes in patients with rheumatoid arthritis.

**References**


Behçet’s disease in Libya

Basma E², Rajab T², Manal Elh¹, Fatma E²

Abstract

Introduction: Behçet’s Disease (BD) is a chronic, relapsing, inflammatory disease characterized by recurrent oral aphthous ulcers and numerous potential systemic manifestations. In Libya, no previous studies were done on BD.

Objective: To study the different clinical manifestations of BD in Libyan patients and compare them with other countries and to compare the behaviour of BD among female and male patients.

Methods: The study was done retrospectively on a cohort of 100 patients with a diagnosis of BD who were registered in our rheumatology clinic in Tripoli Medical Center during the period between 1999 and 2009. The data which were collected from the files of patients included demographic features (such as sex, age at diagnosis and disease duration), different clinical manifestations of the disease which occurred either initially or as a late feature and types of relapses.

Results: One hundred patients enrolled in the study, 71% were male and 29% were female, the ratio of female to male was 1:2.4. The mean age was 31 years. The prevalence of various clinical manifestations were oral ulcers: 100%; genital ulcers: 81%; skin: 42%; ocular: 35%; vascular: 31%; arthritis: 23%; CNS: 32% and positive pathergy test: 21%. The most common initial manifestations of BD on presentation were oral ulcers: 99% and genital ulcers: 80%. The most common late features which occurred after months to years after diagnosis were recorded in 38 patients (38%), were; CNS: 58%, vascular: 31% and ocular: 21%. Relapses occurred in 62% of patients, the most common types were oral ulcers: 60% and CNS relapses: 35%. Eye involvement occurred in 35% and 34% in male and female respectively (p-value=0.89). CNS involvement occurred in 32% and 31% in male and female respectively (p-value=0.94). Relapse rate was 59% in male and 69% in female (p-value=0.35).

Conclusions: CNS manifestations are more common among our patients which is similar to other Arab countries (Egypt and Jordan) but significantly more than other countries like Turkey, some European countries (Italy and Germany) and USA. Male and female have similar prevalence of clinical manifestations (CNS, eye and vascular) and similar relapse rates.

Key word: Behçet’s Disease (BD), Central nervous system involvement (CNS), Relapse

Introduction

Behçet’s Disease (BD) is a chronic, relapsing, inflammatory disease characterized by recurrent oral aphthous ulcers and numerous systemic manifestations, including genital ulcers, ocular disease, skin lesions, neurologic disease, vascular disease and arthritis. BD may have been described by Hippocrates, but was brought to the attention of the modern medical community by Hulusi Behcet’s in 1937. The disease occurs endemically in the eastern Mediterranean and in the middle and far eastern countries, the population deriving from the ancient Silk Road. The highest prevalence was reported in Turkey, with familial occurrences reported from endemic area. BD has a higher prevalence in men than in women. Usually the onset occurs in the third decade of life.

It is rarely seen in children and has more aggressive course in young adults (male). The diagnosis of BD is based on clinical criteria as established by an International Study Group. These criteria omit the less certain and less common features of the disease. Both innate and adaptive immune systems are activated in BD, with a pro-inflammatory and Th1-type of cytokine profile. BD may be linked to a specific primary immune abnormality with a genetic mutation affecting an adhesion molecule or a pro-inflammatory cytokine, which predispose to early or more intense neutrophil and T cell responses. The greatest morbidity and mortality occur with ocular disease (affecting up to two thirds of patients), vascular disease (affecting up to one third of patients) and central nervous system disease (affecting 10-20% of patients). Cutaneous and articular manifestations are common. Renal and peripheral nervous system involvement are less common than in other vasculitides. BD has a highly variable clinical course with recurrences and remissions. In the absence of neurological, ocular and vascular
involvement, the disease is generally benign and with a good prognosis. Blindness, which occurs in up to 25% of the patients, is the major cause of permanent disability. In Libya, the total number of patients with connective tissue disease who were registered in our rheumatology clinic in Tripoli Medical Center from 1999-2009 were 2000 patients. One hundred of them had BD. No previous studies were done in Libya on BD. The primary reason of this study was to know the frequencies of clinical manifestations of the disease in our patients and compare them with other countries and secondly to compare the behaviour of BD among female and male.

Materials and Methods

This study was done retrospectively on a cohort of 100 registered patients with the diagnosis of Behçet’s disease who were registered in our rheumatology clinic in Tripoli Medical Center during the period between 1999 and 2009. All patients were seen by a rheumatologist, ophthalmologist and a dermatologist. Patients were seen by a neurologist when necessary. Diagnosis was based on the clinical picture of the disease and the clinical judgment of at least two rheumatologists and not only on particular diagnostic criteria. The majority of the cases however, were classified by international study group diagnostic criteria. The data which were collected from the files of BD patients includes demographic features (such as sex, age at diagnosis and disease duration), clinical manifestations which occurred at any time of the disease, clinical features which occurred at presentation (initial features) or developed after months to years after diagnosis (late features) and types of relapses (either a relapse of initial features or occurrence of new features). Relapse rates among male and female patients were recorded.

The results were analysed statistically using the Statistical Package for Social Sciences version 11 computer package (SPSS Inc., Chicago, IL., USA). Comparison between clinical features in male and female was done and p-value < 0.05 was considered significant. Comparison between clinical features (eye-CNS-vascular) of our patients with other countries using a graph illustrating a proportion of our patients at the 0 line and percentage of patients using 95% confidence intervals. If the percentage of patients of other countries above 0 line means specific clinical feature in patients of that country more than our patients. If it crosses the 0 line, it means the percentage of clinical feature of patients of that country similar to our patients. If it is below 0 line, it means that the percentage of patients of that country is less than our patients.

Results

The total number of patients registered in our rheumatology clinic in Tripoli Medical Center were 2000. One thousand two hundred (60%) patients had rheumatoid arthritis, 400 (20%) had systemic lupus erythematosus, 200 (10%) patients had systemic sclerosis, 60 (3%) patients had ankylosing spondylitis, 40 (2%) patients had mixed connective tissue disease and 100 (5%) patients had BD.

The mean age of patients with BD was 31 years. The male to female ratio was 2.4:1 and the mean disease duration (duration from date of diagnosis until last review) was 6.6 years. Clinical manifestations of BD which occurred either initially (which present at diagnosis or as late features (which occurred months to years after diagnosis) were distributed as following, oral ulcers in 100%, genital ulcers in 81%, skin involvement in 42% (as acne like lesions 67%, erythema nodosum 28% and folliculitis 26%), eye manifestations in 35% (as posterior uveitis 54%, anterior uveitis 46% and retinal vasculitis 23%), CNS features in 32% (as headache 34%, hemiparesis 31%, cranial nerve palsy 22% and cerebellar ataxia 16%) vascular involvement in 23%, pathergy test was positive in 21% and there was no GIT manifestations occurrence in our patients (Table 1).

<table>
<thead>
<tr>
<th>Country</th>
<th>No.</th>
<th>OA</th>
<th>GA</th>
<th>Skin</th>
<th>Eye</th>
<th>Joint</th>
<th>CNS</th>
<th>GI</th>
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<td>77</td>
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<tr>
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<td>73</td>
<td>86</td>
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<td>80</td>
<td>66</td>
<td>70</td>
<td>42</td>
<td>21</td>
<td>8</td>
<td>19</td>
</tr>
</tbody>
</table>

No.: number of cases; OA: % of oral aphthosis; GA:% of genital aphthosis; Eye: % of ocular lesions; CNS: % of central nervous system involvement; GI:% of gastrointestinal manifestations; Vas:% of vascular involvement.
The most common initial manifestations were oral ulcers (99%). Other initial features occurred as following: genital ulcers in 80%, skin lesions in 45%, eye involvements in 27%, arthritis in 24%, vascular manifestations in 16% and the least common initial manifestations were CNS features 9%. The most common late features which occurred from months to years after diagnosis in 38 (38%) patients, were CNS involvement (22/38) 58%. Other late features were vascular manifestations in 31.5%, eye lesions in 21%, skin lesions in 7%, genital ulcers in 7%. The least common late features were oral ulcers (1/38) 2.6% and no patient developed arthritis as late feature. Sixty two per cent of our patients had relapses (either relapse of initial features or development of new manifestations as late features) and 38% had no relapses. Types of relapses occurred as following; relapse of oral ulcers occurred in 60% of patients, relapse of CNS features occurred in 35.4%, relapse of genital ulcers occurred in 29%. Relapses of skin lesions, eye lesions, vascular involvements and arthritis occurred in 26%, 22.5%, 22.5% and 6% respectively. Clinical features in both male and female were studied and no significant differences were found. They were similar in oral ulcers (100% in both), genital ulcers (86%, 68% respectively), skin features (41%, 44% respectively) and arthritis (21%, 27% respectively) p-value>0.05. Even serious clinical manifestations of BD (CNS, eye and vascular) were similar in male and female. CNS features occurred in 32% of male and 31% of female (P-value=0.9). Eye involvements recorded in 35% of male and 34% of female (p-value=0.06). Vascular manifestations occurred in 37% of male and 17% of female (p-value=0.06). Relapse rate in male was 59% and relapse rate in female was 69% which were also similar (p-value=0.35).

Discussion

Behcet’s Disease (BD) has different clinical manifestations in different countries. This difference might be related to different distribution of susceptibility gene for the disease (HLA B51) in the world. There are many reports on clinical manifestations of BD from different parts of the world10-24. Comparison between clinical features of BD patients in our country and other countries were shown on Table 1.

Regarding CNS manifestations (Figure 1), our patients have a higher frequency of CNS involvement (32%) similar to BD patients in Jordan, Egypt, Saudi Arabia, Iran and England.

Vascular manifestations (Figure 2), in our patients had a frequency similar to Saudi Arabia, Iraq and England patients. Iran has more vascular involvement among their patients. Eye manifestations (Figure 3) in our patients are less than other countries (Iran, Saudi Arabia, Egypt, Morocco, Italy, Germany and England) but similar to Iraq, Jordan, Turkey and USA. Our data show more similarity with those of Jordan, Saudi Arabia and Iraq than with the western parts of the world. Oral aphthae or canker sores are often the initial features of Behcet’s disease25.
causing many of the complications of BD in higher proportion to their female counterparts. But with our patients, we noticed a similar clinical presentations and similar relapse rates in both female and male. Vascular complications develop in about 20-40% of patients with BD. Pulmonary involvement is relatively infrequent, having been reported in 1%-10% of patients. Vascular involvement occurred in 31/100 (31%) of our patients and 2/31 (6.4%) had pulmonary artery aneurysm. They were males and one of them died because of severe pulmonary haemorrhage and the other one is still alive after a left pneumonectomy operation. BD is the most common cause of pulmonary artery aneurysm. Aneurysm formation in the pulmonary arteries indicates a poor prognosis: 30% of patients with this condition will die within 2 years.

**Conclusion**

CNS manifestations are more common among our patients which is similar to other Arab countries (Egypt and Jordan) but significantly more than other countries as Turkey, some European countries (Italy and Germany) and USA.

Both male and female have similar prevalence of clinical manifestations (CNS, eye and vascular) and similar relapse rates.

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Experience with rituximab in patients with rheumatoid arthritis in Nairobi, Kenya

Oyoo GO, Otieno FO, Mbuthia B, Omondi EA, Genga EK

Abstract

Background: Rheumatoid Arthritis (RA) is a disease associated with significant morbidity and mortality. Newer therapies include B-cell targeted therapies such as rituximab.

Objectives: To study the outcome in RA patients receiving rituximab following resistance to Disease Modifying Anti-Rheumatic Agents (DMARDS) and to determine the change in disease activity and functional status.

Methods: A longitudinal prospective study was carried out on RA patients in Nairobi, Kenya. Patients resistant to DMARDS and on rituximab therapy were identified. Their disease activity was assessed using the Simplified Disease Activity Index (SDAI) and the functional status determined using Health Assessment Questionnaire-Disability Index (HAQ DI). The scores were recorded at the beginning of the study then at 3 and 6 months after the initiation of rituximab therapy.

Results: Forty-one patients (36 females and 5 males) receiving rituximab were recruited in this study. At baseline, 18 had moderate and 23 with high disease activity. After 6 months, 7% were in remission, 11% with low, 17 moderate and 6 with high disease activity. There was significant improvement in the SDAI scores witnessed in 13(31.7%) patients in first 3 months and in 22(53.7%) patients after 6 months. There was a significant improvement in the functional and disability score in 95% of the patients after 6 months. There was no significant correlation between the SDAI and the different variables as age, disease duration, type of DMARD and steroids used.

Conclusion: Rituximab use resulted in improvement of disease activity, functional status and disability index in patients with RA in Nairobi.

Keywords: Rituximab, Rheumatoid arthritis, SDAI, HAQI, Nairobi, Kenya

Introduction

Rheumatoid arthritis is a chronic systemic inflammatory disorder characterized by deforming symmetrical polyarthritis often leading to joint destruction, deformity and loss of function. While the exact cause of RA is unknown, multiple different factors interact in genetically susceptible hosts to initiate polyarticular synovitis. The immune mechanisms responsible for the pathogenesis of RA include T and B cells activation, and various inflammatory cytokines. Treatment modalities include Non-Steroidal Anti-Inflammatory Agents (NSAIDs), agents targeting the immune system include steroids, Disease Modifying Anti-Rheumatic Agents (DMARDS), anti-TNF agents and B cell targeted therapies such as rituximab. While NSAIDs, steroids and DMARDS (non-biological) have been the mainstay of treatment since 1970s, newer therapies such as anti-Tumor Necrosis Factor (TNF) agents and B-cell targeted therapies have been more recently introduced.

For early, moderately active RA, drugs used include NSAIDs, steroids and single agents or combinations of non-biological DMARDs, such as hydroxychloroquine (HCQ), sulfasalazine (SAZ), methotrexate (MTX), and leflunomide (LFN). In patients who do not respond adequately to initial DMARD therapy, particularly those with a poor prognosis, treatment with TNF-alpha inhibitors may be considered as an alternative to non-biologic DMARD combination. For patients with persistently active RA (disease of ≥6 months’ duration that has continued despite the use of DMARDS, treatment include the use of biologic DMARDs in combination with non-biologic DMARDs. They usually target specific cytokines or their receptors, such as TNF-α. They may also act as B cell depleting agents and T cell costimulatory blockers.

Rituximab is a non-biological DMARD agent acting on the B cells. It is recommended by the Food and Drug Administration (FDA) in treatment of RA in patients resistant to anti-TNF therapy. It received approval for use in RA in February 2006. In one famous trial known as the REFLEX trial, they randomly assigned 520 patients with...
active RA despite treatment with both MTX and an anti-TNF agent to receive two IV infusions of rituximab one week apart. Mean disease activity, as measured by the disease activity score for 28 joints (DAS28), decreased significantly from baseline over the first four weeks and did not rise after four weeks during the subsequent 20 weeks. In the group receiving MTX and placebo the mean DAS28 rose steadily during the subsequent 20 weeks. Studies have shown it is also effective as first line biological therapy rather than a second line therapy for DMARD resistant RA alone or in combination with other DMARDs such as methotrexate.

Rituximab is a chimeric monoclonal antibody against the CD20 surface marker on B cells. It causes B cell depletion through several mechanisms: Fc receptor gamma-mediated antibody-dependent cytotoxicity complement-mediated cell lysis growth arrest B cell apoptosis. Eliminating B cells decreases production of TNF-α by macrophages, decreases T cell activation and decreases T cell dependent synovial inflammation. A course of rituximab consists of two 500 or 1000 mg IV infusions in combination with methotrexate: an initial dose is administered, followed 2 weeks later by a second dose. Pre-medication with glucocorticoids, and/or antihistamines and antipyretics should be given to lessen infusion reactions. Adverse events in RA include fatal infusion reactions, tumor lysis syndrome, acute respiratory failure, cardiac events, and severe mucocutaneous reactions. The majority of experienced infusion reactions occurs during the first infusion, and includes flu-like illness, fever, chills, nausea, urticaria, bronchospasm, hypotension, angio-oedema, headache and hypoxia. Infusion reactions are most severe with the 1st infusion and lessen with repeated infusions.

The aim of this work was to study the outcome in RA patients receiving rituximab following resistance to DMARDS and to determine the change in disease activity and functional status.

Materials and Methods

Study design: This was a longitudinal prospective outcome study on RA patients failing standard DMARD therapy receiving rituximab. Patients were eligible to the study if they had presented at least 6 months prior with moderate to severe RA despite ongoing treatment with optimal doses of standard DMARDS (MTX, SAZ, LFN, HCQ or combination DMARD therapy). Patients must have failed prior treatment, manifesting as a lack or loss of response to treatment with at least 1 DMARD. Patients who were on concomitant glucocorticoid therapy and/or NSAID were included in the evaluation.

The disease activity was assessed using the Simplified Disease Activity Index (SDAI) and the level of physical functioning and disability was determined using Health Assessment Questionnaire- Disability Index (HAQ DI). Patients who had moderate to high disease activity at six months of follow up were considered to have failed therapy. The study was approved by the local university ethical committee and the study performed in accordance with the ethical standards of the 1964 Helsinki declaration. All patients gave their informed consent prior to their inclusion in the study.

Study treatment: Rituximab was administered by intravenous infusion at 1000mg on days 0 and 15. To mitigate acute drug reaction, methyl prednisone at 100mg was given as premedication, together with 2 tablets of paracetamol and 25mg of promethazine; at days 0 and 15.

Trial end points: The primary study end point was the proportion of patients attaining clinical remission as per the SDAI scoring at months 3 and 6. Secondary and exploratory analyses examined group differences in SDAI improvements among various treatment and demographic categories of patients.

Statistical analysis: All data was collected on the study proforma. Data entry and statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 17. Comparison of means was done using Student’s t test for Mann Whitney U test. Wilcoxon’s matched-pairs signed rank test used to measure the significance of the change from baseline of the SDAI scores.

Results

Patients’ characteristics: Of the 41 patients studied, 36(87.8%) were females and 5(12.2%) were males. The sample comprised of 27 married respondents, 11 were single, 2 were divorced and 1 widowed. Majority (73.2%) of the respondents resided in urban areas and the rest peri-urban. Most (92.7%) of the respondents had attained tertiary level education, 4.9% had attained secondary level of education while 2.4% had no education at all. Thirty respondents were employed and 4 housewives and self employed each while 3 were retired.

The majority (46.3%) of the patients had first RA diagnosis made 5-10 years prior to enrollment. The lowest
percentage (2.4%) of respondents had their first RA diagnosis for less than 1 year. 85.4% of the respondents were on concurrent NSAID therapy. Majority of the patients (78%) had failed MTX or MTX containing combination DMARD regimens. Table 1 summarizes the treatment modalities and the duration of treatment among the studied patients.

**Table 1:** Disease duration and treatments received before commencement of rituximab

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Disease duration (years)</th>
<th>No. (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 - 5</td>
<td>5 - 10</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>MTX</td>
<td>7 (17.1)</td>
<td>19(46.3)</td>
<td>6 (14.6)</td>
</tr>
<tr>
<td>HCQ</td>
<td>8 (19.5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SAZ</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Steroids</td>
<td>10(24.4)</td>
<td>11(26.8)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>35 (85.4)</td>
<td>35 (85.4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>38 (92.7)</td>
<td>38 (92.7)</td>
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</tr>
</tbody>
</table>


**Disease activity in the studied patients:** The mean SDAI decreased significantly (p < 0.001) at 3 and 6 months. There was a significant difference in the SDAI score between 0 and 3 months, 3 and 6 months and between 0 and 6 months, (p<0.001). The SDAI score of the patients are presented in Table 2.

**Table 2:** The Simplified Disease Activity Index (SDAI) at baseline and after 3 and 6 months

<table>
<thead>
<tr>
<th>SDAI score</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>At baseline</td>
<td>2.2</td>
<td>77.8</td>
<td>29.2 ±16.7</td>
</tr>
<tr>
<td>At 3 months</td>
<td>1.9</td>
<td>49.3</td>
<td>21.4 ±12.7</td>
</tr>
<tr>
<td>At 6 months</td>
<td>1.3</td>
<td>34.7</td>
<td>14.4 ±9.3</td>
</tr>
</tbody>
</table>

SDAI: Simplified Disease Activity Index

There were 6 patients remaining with high disease activity at the end of 6 months, as shown in Table 3.

There was no difference in the median of SDAI score across the various categories of time of first RA diagnosis. This implied that improvement in disease activity did not depend on the time of first RA diagnosis. There was consistent decline in SDAI scores irrespective of the time of first RA diagnosis (Table 4).

**Table 3:** Comparison of the number of rheumatoid arthritis patients according to the Simplified Disease Activity Index (SDAI) at baseline and after 3 and 6 months

<table>
<thead>
<tr>
<th>RA patients</th>
<th>Study duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>After 3</td>
</tr>
<tr>
<td>Remission</td>
<td>0</td>
</tr>
<tr>
<td>Low Activity</td>
<td>0</td>
</tr>
<tr>
<td>Moderate Activity</td>
<td>18</td>
</tr>
<tr>
<td>High Activity</td>
<td>23</td>
</tr>
</tbody>
</table>

RA: Rheumatoid arthritis, SDAI: Simplified Disease Activity Index

**Table 4:** Comparison of the SDAI score in RA patients according to the first diagnosis of the disease at baseline and after 3 and 6 months

<table>
<thead>
<tr>
<th>First RA diagnosis</th>
<th>Median SDAI score</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At baseline</td>
<td>After 3 months</td>
<td>After 6 months</td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>12.4</td>
<td>11.7</td>
</tr>
<tr>
<td>1 - 5 years</td>
<td>27.9</td>
<td>17.5</td>
</tr>
<tr>
<td>5 - 10 years</td>
<td>24.1</td>
<td>18.2</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>27.1</td>
<td>21.7</td>
</tr>
</tbody>
</table>

RA: Rheumatoid arthritis, SDAI: Simplified Disease Activity Index

There was significant improvement in the SDAI scores witnessed in 13(31.7%) patients in the first 3 months and in 22(53.7%) patients after 6 months (Figure 1).

**Figure 1:** Percentage of RA patients with significant SDAI change after rituximab therapy for 3 and 6 months

The correlations of the studied parameters with the disease activity (SDAI) are presented in Table 5.
Table 5: Correlation between demographic/treatment variables and disease activity in rheumatoid arthritis patients

<table>
<thead>
<tr>
<th>Variable in RA patients</th>
<th>SDAI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
</tr>
<tr>
<td>Age</td>
<td>0.13</td>
</tr>
<tr>
<td>Disease duration</td>
<td>0.11</td>
</tr>
<tr>
<td>DMARD used</td>
<td>0.24</td>
</tr>
<tr>
<td>Steroid use</td>
<td>0.003</td>
</tr>
</tbody>
</table>

RA: Rheumatoid arthritis, SDAI: Simplified disease activity index, DMARD: Disease modifying anti-rheumatic drug

Functional status: The level of physical disability and functioning improved consistently from baseline to the 6th month in the RA patients receiving rituximab as shown in the Table 6.

Table 6: Level of physical disability and functioning from baseline to 6 months

<table>
<thead>
<tr>
<th>HAQ-DI</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>At baseline</td>
<td>0</td>
<td>3.8</td>
<td>1.19 ±0.8</td>
</tr>
<tr>
<td>After 3 months</td>
<td>0</td>
<td>2.9</td>
<td>0.94 ±0.57</td>
</tr>
<tr>
<td>After 6 months</td>
<td>0</td>
<td>1.9</td>
<td>0.67 ±0.27</td>
</tr>
</tbody>
</table>

The HAQ-DI score at baseline was the highest and decreases with time tending towards a normal curve at the third month (p=0.03). The improvement in functioning and disability was witnessed in the majority (95.1%) patients.

Discussion

It has been confirmed that a single course of rituximab, given as 2 infusions 2 weeks apart, is highly effective over 24 weeks in the treatment of active RA in patients showing incomplete response to standard DMARD therapy\textsuperscript{11}. Rituximab has a novel mode of action that results in the depletion of B cells, and it is therefore distinct from other biologic therapies for RA that target T cells and their related cytokines.

This evaluation of patients receiving rituximab following treatment failure of conventional DMARDS, reviewed 41 patients from Nairobi, Kenya. This study demonstrated significant clinical improvement of patients receiving rituximab both at 3 months and at 6 months. This is consistent with findings from other studies; notably the DANCER trial\textsuperscript{16} which showed significant DAS28 changes from baseline at week 24 in patients receiving both 500mg and 1000mg doses as compared to placebo.

Out of the 41 patients, 6 (15%) had low disease activity at 3 months of follow up with 2 being on remission. At 6 months; 11 (27%) patients had low disease activity with 7 (17%) patients achieving remission. This study compares favorably with results from the study of Nasonov et al\textsuperscript{16} in a prospective cohort biologic register report that noted clinical remission in 12.3% at 6 months with 11.7% having low disease activity.

Disease duration for more than 1 year was significantly associated with changes in SDAI upon rituximab infusion. This was an interesting finding as patients who had less than one year of disease duration did not show significant change in SDAI scores. This could be a selection bias as such patients would have had severe baseline disease activity with poor prognostic indicators resulting in poor outcomes even with rituximab infusion. Pretreatment prognostication is not routinely done in our clinic setting; this would have given us an insight into this cohort. A larger study cohort is required to draw conclusions.

Our study did not establish any significant correlation of clinical response with other variables such as duration of disease, age and type of DMARD therapy used. The DANCER trial similarly did not establish significant effect on ACR20 response in patients who were on concomitant glucocorticoid therapy. However in this study, glucocorticoid therapy was associated with reduced incidence and severity of acute infusion reaction. Our study did not however look at the safety outcomes.

There was an improvement in the mean function and disability as measured by HAQ score. Percinkova et al\textsuperscript{17} demonstrated subjective improvement in functional status with significant decrease in night pain and morning stiffness and decreased number of painful and swollen joints in a similar study of patients with severe, active RA refractory to multiple DMARDS after rituximab therapy.

Our study though had a number of limitations. Our analysis did not scrutinize safety data partly due to short duration of follow-up and missing data on the same. Analysis of long term treatment outcome and safety data is ongoing and shall be reported in future. Many studies have shown that in real life patients move in and out of
remission; thus an analysis of sustained remission (at least 3 months of persistency) would be better.

In conclusion, rituximab infusion resulted in significant improvement of disease activity in patients failing standard DMARD therapy in Nairobi with enhancement in the functional status and disability index.

Conflict of interest: None.

References

Step wise approach of gout in the rheumatology ward of Point-G University Teaching Hospital of Bamako, Mali

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Abstract

Background: Worldwide, the numbers of gout cases are increasing due to behaviour changes and socio economic factors. Although this can be a global health problem according to data reported from industrialized countries, there are limited reports on the disease burden in low and middle income countries like Mali where no data are available. Hence the study was conducted to determine the prevalence and risk factors of gout among Malian patients in a hospital setting.

Methods: This was a descriptive study conducted in the Rheumatology ward of Point-G University Teaching Hospital among out patients visited from January 1st 2009 to February 28th 2010. Using World Health Organization (WHO) step wise approach, a total of 1,143 patients visited, of whom 100 fulfilled the American College of Rheumatology (ACR 1977) criteria of gout. Patients recruited were aged 18 years and above if they provided consent. They were also followed according to the multi parametric step wise approach (step1, step2 and step3).

Results: The prevalence of gout was 17.3%. Patients’ mean (range) age was 57 years (24-75). Women were more affected than men (sex ratio of 1:2) with menopausal women the most affected group (91%). Obesity, high blood pressure, diuretics intake, and kidney failure were observed in 83%, 76%, 64% and 37%, respectively. Clinical manifestations of gout were located in joints (100%), in skin (4 cases of tophus), and kidneys (1 case of nephrolithiasis). Monoarthritis was predominant (36%), especially in the knee (92%). In addition, 95% of patients had hyperuricemia. The main comorbidities were dominated by osteoarthritis, kidney failure, diabetes, and rheumatoid arthritis with 68%, 37%, 13% and 6%, respectively.

Conclusion: The prevalence of gout in our patient was high and overweight/obesity, high blood pressure, diuretics intake and kidney failure were frequent. High prevalence was reported among menopausal women. Although our study was limited, it provided for the first time data on the prevalence of gout and its potential risk factors in Mali. There is a suggestion for further investigation of the disease risk factors.

Key words: Gout, Step wise approach, Epidemiology, Mali

Introduction

Gout prevalence had increased significantly in Europe and United States (1% of total population)1. Similar trend was also seen in emerging countries such as China, Taiwan, and some regions of Oceania (Australia and New Zealand)2 as well as in sub Saharan Africa3. However, easy diagnosis and improved management are lacking. Thus, recommendations on the diagnosis, accurate and prompt management of gout cases have been suggested by European league against Rheumatism (EULAR) in 20054,5 and American College of Rheumatology (ACR) in 20126,7. In developed countries of Europe, the use of these recommendations is limited to only four countries4,5.

In Africa, implementation is limited because of high direct and indirect cost of these recommendations. Thus, the World Health Organization (WHO) recommends the step wise approach for the surveillance of emerging non-communicable diseases8. Step wise approach surveillance of risk factors for non-communicable diseases has been set by intergroup team of WHO in strategic plan of world surveillance settled to observe the tendency of non-communicable diseases in the countries. It is an integrated approach of surveillance, prevention and case management of non-communicable diseases (gout, high blood pressure, diabetes, etc ...). This approach is hierarchical, flexible depending on the needs and the existing systems. It is sequential process that starts with data collection on population health behaviour using a questionnaire. This needs to be
completed by physical examinations, blood samples collection and paraclinical exam.

In Africa, this method had been used to assess risk factors of diabetes (Mali) and high blood pressure (Togo, Benin, Cote d’Ivoire, Cameroon and Congo Brazzaville)\(^9\). The aim of this epidemiological approach was to allow countries to use a compiled data for decision making on planning, public health priorities and prevention strategies generation to allow the reduction of risk factors in order to decrease the epidemic of non-communicable diseases. However, these studies conducted in Africa on non-communicable diseases did not take into account gout, which is also an emerging tropical epidemic. In addition, the main risk factors of gout are similar to that of other non-communicable diseases such as gender, age, iatrogenic causes and food rich of carbon hydrates, alcoholism, high blood pressure, obesity, kidney failure and family gout\(^10,11\). The objective of our study was to assess the prevalence and risk factors of gout among Malian patients in a hospital setting using the WHO stepwise approach.

**Materials and Methods**

**Study site:** This study was conducted in the Rheumatology ward of Point-G University Teaching Hospital of Bamako (Mali). This is the only ward offering rheumatologic care in Mali, and was opened on July 17\(^{\text{th}}\) 2005 with outpatient visit. Inpatient services have been possible since March 19th 2006 with 12 beds. In 2013, the number of outpatient and inpatient visits was 1983 and 75, respectively.

**Study design:** Patients were recruited prospectively from 1\(^{\text{st}}\) January 2009 to 28\(^{\text{th}}\) February 2010. Using WHO Stepwise approach applied to gout and adapted to Malian context, a questionnaire was administered to all participants who consented prior the assessment conducted by one single physician who also performed the three steps of the stepwise approach as described below.

The first step (Step 1) was related to socio demographic information, behaviours, questions on physical activities, nursing hygiene and history (arthritis of the participant or ascendant, renal colic).

The second step (Step 2) consisted of collecting the following physical parameters: measurement of height (cm), weight (kg), blood pressure (mm/Hg), and complete physical exam looking for arthritis tophus and renal colic. Height was measured from wall rod in all participants without shoes or head scarf and weight by spring scale placed on stable surface. These measures were used to determine Body Mass Index (BMI) according to WHO criteria. Blood pressure was measured using standard sphygmomanometer while the patient was lying and subsequently when standing. High blood pressure was based on WHO criteria (systolic blood pressure ≥ 140mm Hg and/or diastolic blood pressure ≥ 90mm Hg).

The third Step (Step 3) consisted of para clinical investigation such as biology, joint liquid, radiography and ultrasound which were feasible in Malian setting. The following biological tests were performed: uricemia, creatinin, fasting blood glucose, blood cells count, Erythrocyte Sedimentation Rate (ESR) and C Reactive Protein (CRP). Hyperuricemia was defined as uricemia level extending 360 µmol/L for woman and 420 µmol/L for man. The normal value of clearance (Cockroft-Gault) was between 60 and 120 ml/mn. Kidney failure was defined as low creatinine clearance (< 60 ml/mn). Diabetes mellitus was defined according to WHO criteria: permanent state of hyperglycemia with fasting blood glucose ≥ 1.26 mg/L (7 mmol/L) twice and/or a random glucose ≥ 2 g/L (11mmol/L). Normal cholesterolemia was between 3.6-6.8 mmol/L. The CRP ≥ 6 mg/L was defined as positive and normal ESR was defined according to Westergren method in adults (Males less than 50 years : < 15mm/h, Males more than 50 years: < 20 mm/h. Females less than 50 years: 20 mm/h, Females more than 50 years : 30 mm/h). Joint puncture was performed to analyse the synovial liquid (research of sodium urate crystals, cytology and culture). As research of sodium urate crystals was not possible in Mali, culture had confirmed the diagnosis in case of severity. The presence of germs in addition to other arguments suggested an infection of gout. Radiography of damaged joints (asymmetric tumours, under cortical cysts, pseudo-osteoarthritis) and face chest (research of infectious foci) was performed. Pelvis ultrasound was done to identify nephrolithiasis. Accurate treatment was administered to each clinical case. The annual cost of gout management was estimated. Gout was defined according to criteria described by the American College of Rheumatology (ACR)\(^12\). Data were entered and analysed using SPSS software version 12.0 and only descriptive statistics were conducted.

**Results**

A total of 1,143 patients were screened in the first step and 198 patients met the inclusion criteria of gout (17.3%), from whom 163 consented. After baseline visit, 63 patients were lost to follow-up and the remaining 100 completed the study (Figure 1).
Figure 1: Study flow chart

1143 patients screened during outpatient consultation

945 did not meet the gout diagnosis

198 patients with gout

63 patients lost to follow up

35 patients refused to participate

100 patients who consented were included

Socio-demographic characteristics of the 100 patients followed are described in Table 1. The most frequent clinical feature was mono-arthritis (36%) and the most location reached was the knees with 92%. Tophus was observed in 4% of which olecranon region of elbow was more affected. Only one patient had renal colic (Table 1). Biological characteristics of gout are recapitulated in Table 2.

Table 1: Socio-demographic and clinical characteristics of gout among patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Male</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Post-menopausal female</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>100</td>
<td>57.32 (10)</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>Tophus</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Renal colic</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Type of arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monoarthritis</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Oligoarthritis</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>Ankle</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Metatarsophalangeal joint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(podagra)</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Wrist</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Elbow</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Shoulder</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Hip</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tophus location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olecranon region of elbow</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Wrist</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Intertarsal joints</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2: Biological features, risk factors and associated pathologies among patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>Anaemia</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Decrease creatinine clearance</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Accelerated erythrocyte sedimentation rate</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Positive C-Reactive protein</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Infected joint fluid</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Unquantified intake of red meat</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Unquantified intake of milk</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>Unquantified intake of eggs</td>
<td>79</td>
<td>79</td>
</tr>
<tr>
<td>Unquantified intake of chocolate</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight/obesity</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Diuretic uptake</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Low-dose acetylsalicylic acid</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Associated pathologies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamid and Ethambutol</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HIV type 1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Hyperuricemia was observed in 95% of patients with a mean (SD) of 526 (130). Decreased creatinine clearance was observed in 37%. Anaemia was observed in 37% and accelerated ESR in 40% of patients. Positive CRP was observed in 42% with a mean (SD) of 22 (53) mg/L. Joint fluid analysis was performed in 12 patients revealed one case of *Acinetobacter calcavari iwofi*. HIV type 1 was found in one patient. Risk factors assessed in all the patients were mostly food habits, overweight/obesity, and diuretics uptake (Table 2). Comorbidity was dominated by high blood pressure (76%), osteoarthritis (68%), kidney failure (37%), diabetes (13%), rheumatoid arthritis (6%) (Table 2). Patients were treated with colchicine (41%) with a mean dose of 1.29 mg per day [1-2 mg], non-steroid anti-inflammatory drug (76%) for treatment of acute crisis and the allopurinol (64%) with a mean dose of 326.5 mg per day [100- 600 mg] as Urate-Lowering Therapy (ULT). All the patients were advised to eat poor purines food. In 99% of patients, clinical improvement was observed after 2 months.
However, a case of skin reaction was seen in a patient on allopurinol. Thus, he received ascorbic acid (500 mg per day) treatment as alternative. The mean annual cost (drugs and analysis) of gout management was estimated to be US$330.83.

Discussion

This present study examining the prevalence and risk factors of gout was the first epidemiological descriptive study of gout in Mali. The screening of the patients in hospital could be the limit of the extrapolation of the study findings to the general population.

The reported prevalence of gout in our study was higher than that reported (4.9%) in the same hospital in 2006\textsuperscript{13}. This suggested an increased prevalence of the disease. As the Department of Rheumatology was opened only in 2006, this increase may be explained by the increase in rheumatology activities enhanced by qualified personnel in rheumatology in Mali from 2006 to 2010. The same explanation could be evoked in Togo where the prevalence reported in 2000 was lower (1.9%)\textsuperscript{14}. Our observation of 3% of gout before 40 years old is in accordance with previous findings of the scarcity in childhood\textsuperscript{15}. The mean (SD) age of our gout patients was 57.3 (10) years and only 3% had less than 40 years. Also, 50 of the 55 women recruited were in menopause. These supported findings that gout is more frequent in elderly and menopausal women\textsuperscript{15}. However, our results of higher prevalence of gout in females (55%) was different from that reported by the same author suggesting higher prevalence in male\textsuperscript{15}. The high prevalence of gout in menopausal women can be explained by the protective uricosuric effect of estrogen during childbearing age\textsuperscript{16,17}. Study conducted in Taiwan suggested that alcoholism in men, and menopause before 60 years were associated with gout, while kidney failure and diuretic uptake were important risk factors after 60 years\textsuperscript{18,19}.

The consumption of alcohol was low (5%) in our study. However, alcoholism was found in 79% of the gout patients in South Africa, and 83% in Togo\textsuperscript{1} suggesting that alcoholism may contribute to the occurrence of gout, probably due to hyperuricemia associated with high alcohol consumption as reported by other authors\textsuperscript{16}. The same authors reported that the consumption of animal proteins is an important contributor to gout. This corroborated our study where 100% of our patients ate red meat. Overweight/obesity was observed in 83% of the patients, and this was more frequent among women (56.4%). This can be explained by factors such as high urbanization, physical inactivity, feeding habits, and social cultural handicap (obesity as criteria of opulence) as suggested elsewhere\textsuperscript{13,19,20}. The prevalence of high blood pressure observed in our study (76%) was similar to that reported by Seyni\textsuperscript{12} in 2006 in Mali with 76.7%. This was higher than that observed in Togo with 26.3% in 2000\textsuperscript{14}. The increase in frequency of high blood pressure observed in gout patients is supported by the several hypotheses among which the decrease in kidney perfusion leading to the reabsorption of uric acid, and the ischemia due to arteropathy which also lead to cell destruction, DNA and ARN releasing, and ATP degradation. Thus, an increase in the synthesis of uric acid is observed\textsuperscript{21,22}. As hyperuricemia can be suggested to cause high blood pressure and vice versa, the study was not able to demonstrate the temporal relationship between the two conditions. The uptake of diuretic found in 91.9% of our patients with high blood pressure is also in conformity with the literature. This can be explained by the decrease of urinary excretion of uric acid\textsuperscript{23}.

In general, the clinical description of gout in our study was similar to that reported from other countries of sub-Saharan Africa and developed countries\textsuperscript{13}. However, monoarticular topography in the knee (92%) followed by ankle (45%) was predominant in our study compared to other authors reporting hallux monoarticular localization as the most common\textsuperscript{14,24}. As suggested by previous authors\textsuperscript{17}, our study found that polyarticular localization was more common in elderly women and subjects with diuretic uptake. Similar to other African series\textsuperscript{1}, our study found only 4% of tophus and 1% of nephrolithiasis. This scarcity has been described as very specific to gout in tropical areas\textsuperscript{1}.

As described elsewhere\textsuperscript{25}, the risk of gout increases with the duration and the rate of hyperuricemia. This is supported by our findings that 95% of patients had hyperuricemia with a mean of 526.40 µmol/l. High mean uricemia in gout patients was also reported in an earlier study in Mali\textsuperscript{13} and in Togo\textsuperscript{14}. However, other authors suggested that only 10% of subjects with hyperuricemia develop gout due to non-identified factors\textsuperscript{26}. Although 37% of our patients had kidney failure, the design of our study is not able to demonstrate the relationship between kidney failure and hyperuricemia as established earlier with blur temporal relationship\textsuperscript{25,27}.

The association of gout, obesity and high blood pressure is very strong in sub Saharan Africa\textsuperscript{14}. According to the literature, coexistence between gout and rheumatoid arthritis is rare\textsuperscript{28,29}. This corroborates our study with 6% (6 cases). However, the authors reported that 10% of patients with rheumatoid arthritis should develop hyperuricemia and 30% of patients with tophi gout should also have low titer of rheumatoid factors. In addition to the scarcity of the coexistence between the two conditions, true coexistence criteria is difficult to assess as suggested by Wallace et al\textsuperscript{30}. Criteria for true coexistence of rheumatoid arthritis and gout should include seropositive, erosive rheumatoid arthritis with histologic confirmation of nodules, with or without extra articular manifestations; acute gouty attacks with documented deposits of monosodium urate crystals in either synovial fluid or tophi; and responsiveness to treatment with colchicine.

For the treatment of gout, new recommendations were suggested by the ACR in 2012\textsuperscript{6,7}. However, as our study was conducted prior to these recommendations, classic treatment of gut was used. It consisted of poor regimen in purines, colchicine, non-steroid anti-inflammatory drug, and allopurinol. Ascorbic acid was used as alternative to allopurinol in case of intolerance as suggested earlier\textsuperscript{20}.

Conclusion

The prevalence of gout in our patients was high; overweight/obesity, high blood pressure, diuretics, and kidney failure were frequent. High prevalence was
References


Research article

Anaemia in patients with rheumatoid arthritis at the Kenyatta National Hospital, Nairobi, Kenya

Muia GM¹, Oyoo GO¹, Kitonyi GW², Wanzala P³

Abstract

Background: Anaemia is the commonest extra articular manifestation of Rheumatoid Arthritis (RA). Anaemia is an independent predictor of morbidity and mortality in the population. When RA is complicated by anaemia it is associated with a more severe disease and significant reduction in the quality of life in the affected patient.

Objectives: To determine the characteristics and the prevalence of anaemia in patients with RA at the Kenyatta National Hospital (KNH) and correlate the anaemia with the disease activity using the Modified Disease Activity Score 28 (MDAS28).

Design: A cross sectional descriptive study.

Methods: Patients presenting to the Rheumatology Outpatients Clinic (ROPC) in Kenyatta National Hospital were screened and those who met the American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) diagnostic criteria for RA were consecutively recruited to the study. The study period was 6 months from September 2011 to March 2012. Consecutive sampling technique was applied until the desired sample size was achieved.

Results: Ninety seven patients were studied in a span of six months (September 2011 –March 2012). Females were 84 (86.6%) while males were 13 (13.4%) with a male to female (M: F) ratio of 1:6.8. The mean age of the study population was 50.7 years with age range of 18-88 years. Seventy nine percent of the patients had the clinical features of RA for more than one year while 69% had the diagnosis made in the last five years. Eighty percent of the patients were on methotrexate while 72% were on Non Steroidal Anti Inflammatory Drugs (NSAIDS). The mean haemoglobin was 12.4 g/dl with a range of 3-15.7g/dl. Thirty three percent of the patients had high disease activity while 57 (58.8%) had moderate disease score. The prevalence of anaemia in the study population was 33% with Anaemia of Chronic Disease (ACD) responsible for 75% of the cases of anaemia while Iron Deficiency Anaemia (IDA) was seen in 25% of the cases. Anaemia was commonly seen among the patients with high and moderate disease activity scores. None of the patients on remission and low disease scores had anaemia. Anaemia was also found to be independently related to the disease activity and the patient’s gender with males being the most affected.

The use of Disease Modifying Anti Rheumatic Drugs (DMARDs) was found to confer protection to anaemia. The study did not demonstrate any significant association between the use of NSAIDs and use of steroids and IDA.

Conclusions: There is a high burden of anaemia in RA patients although it is lower compared to studies done elsewhere. Anaemia correlates very well with the disease activity. Anaemia of chronic disease is the commonest type. The use of DMARDs was associated with reduction of anaemia among the patients.

Keywords: Anaemia, Rheumatoid arthritis, Kenyatta National Hospital

Introduction

Rheumatoid Arthritis (RA) is a chronic, symmetric, peripheral poly-arthritis of unknown aetiology which when untreated or if unresponsive to therapy, typically leads to deformity and destruction of joints through a persistent inflammatory synovitis. This leads to eventual erosion and destruction of cartilage and bone which form the joints. As with other autoimmune rheumatic diseases, the diagnosis depends upon
Anaemia is also associated with impaired cognitive performance, depressive symptoms, physical function, including increased frailty, muscle weakness, and falls. Anaemia is also associated with impaired cognitive performance, depressive symptoms, and reduced quality of life.

The commonest anaemia seen in RA is the classical model case of anaemia caused by chronic disease being mostly of the normocytic normochromic type; it is multi-factorial, reflected in the dimorphic appearance and wide red cell distribution width. Iron Deficiency Anaemia (IDA) is the other important type of anaemia in RA and it manifests with a microcytic hypo-chromic picture.

Borah and colleagues in a study in Northern India found a prevalence of 64% among patients who had been on follow up with RA for a period of more than 2 years and in this cohort 65% of the anaemia observed was ACD while IDA accounted for 33% of the anaemia observed. In 1997 Davis et al. studied 64 patients who were newly diagnosed to have RA attending an outpatient clinic in London and found an incidence of 61%, ACD accounted for 67% of the causes. Literature search does not yield any studies done in Africa on the prevalence of anaemia in this patient population. There is evidence that the patients who are anaemic have more severe RA, and also have more affected joints and higher levels of functional disability and pain. Anaemic patients, particularly those with Anaemia of Chronic Disease (ACD), have a significantly greater number of the American College of Rheumatism Criteria (ACR) for RA, significantly more erosive joint damage, and significantly increased concentrations of serum rheumatoid factor than patients without anaemia.

In our study we set out to establish the burden of anaemia among RA patients seen in Kenyatta National Hospital (KNH) Rheumatology Outpatients Clinic (ROPC) and determine how the severity of anaemia related to the disease activity. The study was designed to determine the prevalence of anaemia in this patient population, classify the anaemia types the patients had and correlate the same with the patients socio-demographic variables, disease activity using the modified disease activity score (MDAS28), patients level of education, duration of illness, the type of medication used and the duration of treatment.

**Materials and Methods**

The study design was a hospital based cross sectional descriptive study at the Rheumatology Outpatient Clinic, Kenyatta National Hospital. The study was commenced after obtaining all the necessary ethical approvals from the KNH research and ethics committee and from the Department of Clinical Medicine and Therapeutics, University of Nairobi. All patients above 18 years seen at KNH rheumatology clinic that met the ACR-EULAR criteria for diagnosis of rheumatoid arthritis were eligible. All patients gave an informed written consent. The study excluded patients with known hereditary forms of anaemia, patients with RA and mixed connective tissue diseases or SLE and also those with chronic liver and renal disease. The minimum sample size was calculated to be 96 patients.

Consecutive sampling method was applied. Anaemia in our study was defined as per the WHO parameters of haemoglobin of less than 13g/deciliter for males and 12g/deciliters for females. Anaemia of chronic disease was defined as normocytic normochromic anaemia with serum ferritin levels above 50g/l. Iron deficiency anaemia was defined as patients with hypochromic microcytic picture on PBF and MCV less than 76g/deciliters and serum ferritin levels below 50g/liter. Recruited patients were evaluated by medical history as per the study questionnaire. The disease activity was determined using a validated standardized tool the Modified Disease Activity score 28 (MDAS 28).

Physical examination was carried out looking for stigmata for diseases in the exclusion criteria and disease activity was determined using MDAS28 questionnaire.
Then blood was drawn for the appropriate laboratory tests. Data was collected and entered into a computer data base then cleaned and verified. Statistical analysis was done using SPSS version 17 software. Descriptive statistics –proportions were used for categorical variables. Measures of central tendencies were used for continuous variables. Correlation was done using the Spearman’s -Rho correlation coefficients. Multivariate analysis was done using linear regression. Statistical significance was a P-value of ≤0.05.

Results

In a period of 6 months (September 2011 – February 2012) 108 patients with RA were identified, of these 103 met the EULAR-ACR criteria for RA and were recruited to the study. Three patients had RA with mixed connective tissue disease/ SLE and were duly omitted. One patient was recruited but declined to give consent to have blood tests done. Two patients did not have their ESR done hence were excluded from the final analysis. Hence results from 97 patients were analysed. A summary of the demographic characteristics of interest in the study population are shown in Table 1.

Table 1: Characteristics of the study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency (%) (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50.7 (17.8)</td>
</tr>
<tr>
<td>Age groups</td>
<td>18-88</td>
</tr>
<tr>
<td>&lt;30</td>
<td>13 (13.4)</td>
</tr>
<tr>
<td>30-49</td>
<td>28 (28.9)</td>
</tr>
<tr>
<td>50-69</td>
<td>40 (41.2)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>16 (16.5)</td>
</tr>
<tr>
<td>Gender</td>
<td>13 (13.4)</td>
</tr>
<tr>
<td>Male</td>
<td>84 (86.6)</td>
</tr>
</tbody>
</table>

The mean age of the entire patient population was 50.7 years with a range of 18 - 88 years. The peak age group was 50-69 years who constituted 40% of the study population. Majority of the patients (86.6%) were females. There was an almost equal mix of the patient population from rural and urban setting. Nairobi and its environs contributed 49.5% of the total population while Central Kenya contributed 32% of the patients reflecting the traditional catchment area of Kenyatta National Hospital. From the patients’ history and evaluation around 79% of the patients had the symptoms of RA for a period of longer than 1 year before a diagnosis was made, whilst 69% of the patients had been diagnosed with RA in the last 5 years. Figure 1 is a summary of patients history and duration of RA.

The commonest drug used by the patients was methotrexate seen in 80% of the study population while 72% of the patients were regularly on NSAID. It is worth noting that 100% of the patients who were on methotrexate were on supplementation on a daily basis as depicted in Figure 2.

The mean haemoglobin was 12.4g/dl with a range of 3.0-15.7g/dl. The mean haemoglobin for females was 12.5g/dl with a median (IQR) 12.9g/dl (11.9-13.7). While the mean haemoglobin for males was 11.8 g/dl with a median of 12.7g/dl and IQR-(11.3-13.5). The mean serum ferritin was 73.3mg/l with a range of (6.9-1977mg/l). The prevalence of anaemia was 33% (95% CI 23.6-42.4%) in the study population. 24.7% (95% CI 16.1-33.3%) of the patients had Anaemia of Chronic Disease (ACD) while 8.3% (95% CI 2.8-13.8%) had Iron Deficient Anaemia (IDA) as depicted in Figure 3.
The modified disease activity score 28 showed that most patients had moderate to high disease activity with 58.8% of the patients having moderate disease activity while high disease activity was seen in 33% of the patients. Only 4% of the patients were on remission and another 4% had low disease activity. The relationship between the presence of anaemia and the MDAS28 in the study population is summarized in Table 2.

Table 2 : Comparison of MDAS 28 among the patients and anaemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. with anaemia (%)</th>
<th>No. with normal Hb (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (&lt;2.6)</td>
<td>0 (0.0)</td>
<td>4 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Remission (2.7-3.2)</td>
<td>0 (0.0)</td>
<td>4 (6.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate (3.3-5.1)</td>
<td>10 (31.3)</td>
<td>47 (72.3)</td>
<td></td>
</tr>
<tr>
<td>High disease activity (&gt;5.1)</td>
<td>22 (68.8)</td>
<td>10 (15.2)</td>
<td></td>
</tr>
</tbody>
</table>

There was a trend of increased chance of being anaemic as the disease activity score increased from remission to high disease activity. Being male was significantly associated with being anaemic with a P-value of 0.008. There was no significant association of anaemia with the patient’s age, the level of education or the time since the diagnosis of RA. Findings are summarized in Table 3.

Table 3 : Association of anemia with disease duration

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anaemia</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration since diagnosis of RA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 1 year</td>
<td>9 (30.0)</td>
<td>21 (35.9)</td>
<td>1.0</td>
</tr>
<tr>
<td>1-5 years</td>
<td>13 (43.3)</td>
<td>20 (31.3)</td>
<td>2.3 (0.6-9.1)</td>
</tr>
<tr>
<td>More than 5 years</td>
<td>8 (26.7)</td>
<td>21 (32.8)</td>
<td>2.4 (0.5-12.3)</td>
</tr>
</tbody>
</table>

*Association of anaemia with treatment:* The study results demonstrated that the use of DMARD was associated with reduced likelihood of patients being anaemic. The introduction of any DMARD medication was protective of anaemia (P value of 0.012). The use of methotrexate alone or in combination was significantly associated with reduced possibility of patients getting anaemia p value (0.044). The findings can be attributed to the control of the disease which the DMARDs confer to the patients leading to reduction of the chronic inflammation (Table 4).

Multivariate analysis of factors associated with anaemia:
The study demonstrated that gender and age were independently associated with anaemia after analysis.

**Discussion**

Anaemia in RA is associated with increased morbidity and mortality. Anaemic patients have also been shown to have poor quality of life. There is evidence that prompt diagnosis and institution of appropriate treatment leads to better health among the affected individuals. Literature search does not yield any studies done in Africa on anaemia among patients with RA hence the findings of the study will shed light on the burden and the findings can be used to improve patient care. The total number of patients identified in a span of 6 months was 108 out of which 103 patients met the strict ACR-EULAR CRITERIA for RA. This number is almost double (n=65) of what Owino et al found in 2008. This is an indication of the rise in the patient numbers in the recent past after enhanced patients awareness of RA and starting of specialized ROPC.

The study population was middle aged with a mean age of 50.7 years. The highest proportion of patients were above 50 years (56%). This mirrors favorably with worldwide epidemiologic data on RA which peaks from the 5th decade of life. The M: F ratio of RA in the patient population was at 1:68, this was lower than the universally published ration of M:F of 1:3; however the study still demonstrated that RA burden like other connective tissue is still highest among the female population.
There was a delay before diagnosis of RA was made with 79% of patients reporting to have had signs and symptoms of the disease for a period of over one year while 69% had the proper diagnosis made in the last one year only. The reasons given for delayed diagnosis was management in other peripheral facilities and use of NSAIDs which patients reported to give them some relief. Literature search did not yield any other studies to compare the average span of time patients take before diagnosis and its effect on treatment outcomes.

Ninety two percent of the patients had been started on DMARDs with methotrexate being the drug of choice seen in 76% of the total population; 55.9% of them had been on methotrexate for a period of over one year. Agrawal in India found only 49% of patients used methotrexate22. The popularity of methotrexate can be attributed to its simple dosing regimen of once a week, affordable cost, its proven benefits in reducing the chronic inflammation in RA. The two factors lead to improved compliance to the treatment.

The prevalence of anaemia in the study was 33% of the study population. This is lower compared to other studies done in a developing country specifically India. Borah et al23 studied patients who had been diagnosed to have RA in the past 2 years in a rural Northern India and found a prevalence of 64%. while Agrawal et al22 still in Lucknow India found a prevalence of 70.6% when he did a 2 year prospective follow up of 214 patients with RA. Possible reasons for the differences can be due to the study design and difference in study populations being compared. The two studies from India looked at patients who had had RA in a span of less than 2 years while in our study 65% of the patients had RA for a period of more than one year meaning most had been started on appropriate treatment to control the disease. In addition, Agrawal et al22 did a two year prospective study. Another plausible reason for the difference in the findings may be attributed to the high prevalence of anaemia in India at almost 50% in the rural areas as compared to Kenya with a prevalence of around 38% according to the WHO global data base on anaemia burden22. The study showed that 75% of the cases of anaemia were ACD while IDA accounted for 25%. The findings compare well with other studies done in other centers. Borah et al23 study in India found a prevalence of 65% and 33% respectively for the two main forms of anaemia in RA. The high prevalence of ACD can be explained by inadequate control of the disease as it was found that ACD was the common form of anaemia in those patients with moderate and high disease activity. Delayed diagnosis is also a possible major contributing factor of the high ACD burden. The study did not demonstrate any significant association between IDA and use of NSAIDs and use of steroids (P value 0.870); however the patients who had been on NSAIDs for more than one year were likely to have anaemia (P value 0.033). Paradoxically the predominant anaemia was still ACD as opposed to IDA which would have been the expected finding at 74% and 26% for ACD and IDA respectively (n=19). This could possibly be explained by regular prescription of proton pump inhibitors among the patients on long term NSAID prescriptions and also the failure of clinicians to adequately adjust patients treatment once resolution of the severe presenting symptom of pain seen in RA has resolved.

**Anaemia and disease activity score:** There was a statistically significant relationship between the disease activity and occurrence of anaemia (P < 0.001). Multivariate analysis also found that the disease activity was independently associated with anaemia. Similar findings have been reported by others, Agrawal et al22 found anaemic patients had severe disease activity with a mean MDAS of 5.3 compared to non anaemic patients who had moderate disease activity (3.3-5.1) with mean disease activity of 3.83. Borah23 demonstrated that there was an inverse correlation between haemoglobin level and the disease activity score.

The study also demonstrated that the MDAS28 scores were higher in patients with ACD with an average score of 5.6 which correlates with high disease activity score. The mean MDAS 28 in patients with IDA was 5.3. Agrawal22 found patients with ACD had average disease activity of 5.69 while those who had IDA had an average disease activity of 4.7. Anaemia tended to be commoner among males with 45% of them being anaemic (P<0.008); this finding in our study has not been reported in literature elsewhere. The finding could be by chance due to the small number of patients studied although multivariate analysis showed this variable to be independently associated with anaemia. Other possible explanations to this finding could be poor health seeking behaviour in males and delay in diagnosis of RA in males with 3 male patients having had arthritis symptoms for over 5 years before diagnosis.

The use of NSAIDS was not significantly associated with anaemia. Of the anaemic patients 22(71%) were on a NSAID vs. 72.6% of patients on NSAIDs who had normal haemoglobin n=45 (P 0.870). The initiation of any DMARD reduced the likelihood of anaemia (P value-0.044). Methotrexate alone reduced the chance of patients being anaemic (P value-0.012). Methotrexate alone reduced the chance of patients being anaemic (P value-0.044). Sub group analysis of steroids and hydroxychloroquine did not show a significant association with anaemia. The introduction of DMARDS /methotrexate leads to control of the inflammatory process hence this protects the patients from being anaemic23.

**Conclusions**

There is still a high burden of anaemia in our RA patients although it is lower compared to other areas. Anaemia correlates with the disease activity and those patients with anaemia tend to have high disease activity scores and the commonest anaemia type in this group is ACD.
which means the disease control is still not adequate. Introduction of DMARDs is associated with reduction of the incidence of anaemia hence they are protective from both the disease and its complications. Men form a small percentage of patients with RA and when they present they have more severe disease and severe anaemia.

**Study limitations**

Recall bias was a major challenge encountered. This may affect the reporting of onset of disease symptoms. Other causes of anaemia can be confounders. The study was cross sectional in nature and it involved a highly pre-selected patient population being seen in a referral tertiary institution hence the findings may not be reflective of the total population. Serum ferritin though is a proven marker to estimate the level of iron store its being an inflammatory marker may be elevated by other causes.

**Recommendations**

A bigger multicenter African study is recommended and this should include a larger male patient population to confirm the findings of a high prevalence of severe anaemia in this gender are recommended. ACD being the commonest form of anaemia means that we have to enhance care of patients and retard the chronic inflammation which is the hallmark of RA and through this the burden of anaemia will be reduced. Increased surveillance for anaemia and early introduction of DMARDs in patients with RA.

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Abstract

Objective: To determine the anatomical aspects and results of surgical treatment of herniated disk and lumbar spinal stenosis observed in the Rheumatology unit of CHU SO of Lomé.

Patients and methods: This was a transversal study conducted on a series of patients cases admitted to the Rheumatology Unit of CHU SO of Lomé and who underwent surgery for a herniated disk or lumbar spinal stenosis.

Results: One hundred and two patients (37 women, 65 men) were included in the study: 30 (8 women, 22 men) underwent surgery for a herniated disk and 72 (29 women, 43 men) for a lumbar spinal stenosis. Both diseases have occurred in individuals in the prime of age, 92 (90%) with an age between 40 and 60 years. The time between the intervention and the evaluation of the treatment was 9 years on average for the herniated disk and 13 years for the lumbar spinal stenosis. Herniated disk occurred in discs L4L5 and/or L5S1. Lumbar spinal stenosis was showing a rosary image. The responsible factors for the narrowing were hypertrophy of the yellow ligament, posterior inter-apophysis osteoarthritis and degenerative disc disease. The outcome of surgical treatment was satisfactory in 29 of the 30 patients operated on for herniated disk, and 70 of the 72 were operated on for lumbar spinal stenosis. Herniated disk occurred in discs L4L5 and/or L5S1. Lumbar spinal stenosis was showing a rosary image. The responsible factors for the narrowing were hypertrophy of the yellow ligament, posterior inter-apophysis osteoarthritis and degenerative disc disease. The outcome of surgical treatment was satisfactory in 29 of the 30 patients operated on for herniated disk, and 70 of the 72 were operated on for lumbar spinal stenosis. It has resulted in the disappearance of the nerve root pain and the resumption of normal activity. Low back pain requiring the use of analgesics was present in 40 of 102 patients (39%). Twenty patients, including 10 of the 15 who underwent fusion made use of a lumbar belt. Two patients were subjected to reoperation. Spondylodiscitis complicated the postoperative course of one female patient.

Conclusion: Our results are very similar to those described in the literature both on anatomical aspect and therapeutical aspect.

Introduction

Studies conducted in sub-Saharan Africa over the past three decades have established the epidemiologic and semiological profiles of lumbar herniated disk and lumbar spinal stenosis. These studies have contradicted earlier data, especially those from Southern Africa, marred by methodological bias. Lumbar herniated disk is of a profile in every way comparable to that observed in the West; the only semiological peculiarity is the frequent normality of Schöber index, due to lumbar hyperlordosis, characteristic of the morphotype of black subjects; this anatomical data also appears to play a role in the occurrence of lumbar spinal stenosis, which seems much more frequent than in the West, and preferentially affects obese women over 50 years. In sub-Saharan Africa, the risk factors of lumbar spinal stenosis do not seem to be the same with those described in the West where the disease predominates in obese men engaged in hard work.

The treatment of lumbar herniated disk and lumbar spinal stenosis is always medical, surgical sometimes. In the West, it has been subject of evaluation through metrology. This evaluation is particularly focused on pain by taking into account the intensity, the topography, the real life, the perceived, and the socio-professional consequences.

Few studies in sub-Saharan Africa were conducted to decrypt anatomical aspects and to evaluate the surgical treatment of these conditions. This study conducted in a hospital in sub-Saharan Africa aims to describe the anatomical aspects of lumbar herniated disk and lumbar spinal stenosis and to evaluate the results of surgical treatment at mid and long term in patients operated for these conditions.

Materials and Methods

This was a transversal study conducted on a series of patients cases admitted to the Rheumatology Unit of Sylvanus Olympio Teaching Hospital (CHU SO)
of Lomé and who underwent surgery for a herniated disk or lumbar spinal stenosis. The study was conducted from 1990 to 2012. CHU-SO, the largest health facility in Togo, has 847 beds with an average occupancy rate of 54%. In 2010, 68807 patients were managed out of which 21370 were admitted. Lomé, capital city of Togo, where CHU-SO is located, has 900000 inhabitants, and Togo 6200000. The income per inhabitant is about USD 400 in Togo. Only government employees have been benefiting from medical insurance for the past two years.

The Rheumatology Unit of CHU-SO shares with that of Dermatology unit two pavilions with a total capacity of 28 beds. It opened in October 1989 and hosts an average of a thousand consultants per year. Service staff consists of a Professor in rheumatology, two clinic head assistants, two doctors, a supervisor, two nurses, three nursing assistants and a secretary.

The patients included in the study underwent surgery for herniated disk or lumbar spinal stenosis. The diagnosis of these conditions was based on clinical data and morphological data (standard X-ray, myelography, CT scan, magnetic resonance imaging). The imagery of these conditions was based on myelography until 1998, date of implementation of the first scanner in Lomé. The cost of the scan for lumbar spine is 60000 CFA (USD 120), and that of MRI, established in 2006, ranges from 150000 (USD 300) to 280000 CFA (USD 560). The patients we could not contact for the collection of information necessary for the evaluation of their treatment were excluded from the study. It was the same with those whose operative report did not include detailed anatomical data according to the study protocol.

Preoperative parameters taken from the records included demographic data (name, age, sex, occupation, address, duration of disease progression before surgery) and semiological data (low back pain, nerve root pain, paresthesia, walking distance, objective sensory disturbances, motor disorders, sphincter disorders, drug treatments, use of lumbar belt, standard X-ray, myelography, scan, magnetic resonance imaging). The operation data and the nature of surgical treatment were taken from operation reports. The patients were operated in Togo or abroad (Benin, Côte d’ivoire, Morocco, Senegal, France, Switzerland, United States of America).

The collection of the results of the surgical treatment was based on the use of records of the patients included in the study. The data collected were primarily clinical, made of symptoms and opinion of the patients. Only standard X-ray of the lumbar spine in front and in profile was systematically performed postoperatively in all patients, which was not the case neither with the scan nor with the MRI.

Results

One hundred and two patients (37 women, 65 men) were included in the study. Thirty (8 women, 22 men) underwent surgery for a herniated disk and 72 (29 women, 43 men) of lumbar spinal stenosis. Both diseases occurred in individuals in the prime of age, 92 of them (90%) with an age range between 40 and 60 years (Tables 1 and 2).

Table 1: Demographic data of the 72 patients operated for a lumbar spinal stenosis

<table>
<thead>
<tr>
<th></th>
<th>Average age at consultation (years)*</th>
<th>Duration of the progress of the disease before intervention (years)*</th>
<th>Duration of follow up (years)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (n=29)</td>
<td>49 (32-67)</td>
<td>6.7 (1-16)</td>
<td>7.2 (0.5-14)</td>
</tr>
<tr>
<td>Male (n=43)</td>
<td>58 (33-78)</td>
<td>5.3 (0.5-24)</td>
<td>10 (0.5-20)</td>
</tr>
<tr>
<td>Total (n=72)</td>
<td>54 (32-78)</td>
<td>5.8 (0.2-24)</td>
<td>8.9 (0.5-20)</td>
</tr>
</tbody>
</table>

*the first number indicates the average, and the numbers in brackets indicate the limits.

Table 2: Demographic data of the 30 patients operated for a herniated disk

<table>
<thead>
<tr>
<th></th>
<th>Average age at consultation (years)*</th>
<th>Duration of the progress of the disease before intervention (years)*</th>
<th>Duration of follow up (years)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (n=8)</td>
<td>44.3 (40-49)</td>
<td>1.4 (0.2-10)</td>
<td>18 (7-20)</td>
</tr>
<tr>
<td>Male (n=22)</td>
<td>43 (32-53)</td>
<td>2.4 (0.1-6)</td>
<td>10.8 (1.5-25)</td>
</tr>
<tr>
<td>Total (n=30)</td>
<td>43.3 (32-49)</td>
<td>2.1 (0.1-10)</td>
<td>12.7 (1.5-25)</td>
</tr>
</tbody>
</table>

* the first number indicates the average, and the numbers in brackets indicate the limits.

In 21 of the 72 patients operated on for LSS, imaging was based on myelography which showed a rosary image in all cases. These were patients admitted before installation of the scanner in Lomé. Thirty-five patients benefited from the scan, and the other 16 benefited from both a lumbar scan and a lumbar MRI. This is the case of patients especially who underwent lumbar fusion. In all cases, the decision for operation was justified by a perfect radio-clinical correlation. Lesions objectified by imaging and responsible of narrowing revealed a degenerative disease in 72 patients, and this was even among the youngest two, aged respectively 32 and 33 years at consultation. The patients aged 32 years suffered seven years of mechanical low back pain, complicated for a year by the addition of a claudicant lumbar nerve root pain limiting walking within 500 meters. This lumbar nerve root pain was associated with paresthesia. The scan showed a spondylolysis L4 with grade I anterolisthesis, and stepped disc protrusions. The intervention consisted...
of a complete L4 and L5 and partial L3 laminectomy, removal of hypertrophied yellow ligament, abrasion of articular facets and L4L5 diskectomy. In this patient, the surgical report also stated total absence of epidural fat.

Patients aged 33 years and free from any significant pathological history, the narrowing of the spinal canal was related to a discal degenerative affection which created for two years a claudicant lumbar nerve root pain limiting walking within 500 meters. The myelography showed a rosary image with two herniated discs in L3L4 and L4L5. The scan also objectified stenosis in the anteroposterior and malunion of the right pedicle of L4. The intervention consisted of a right L3L4L5 hemi-laminectomy, an L4L5 and L3L4 diskectomy, and of a foraminotomy.

The lesions responsible of the narrowing of the canal observed intraoperatively in patients operated on for LSS included a hernia or disc protrusion (31 cases), hypertrophy or shortness of blades (67 cases), hypertrophy of the yellow ligament (27 cases), a posterior inter-apophysis osteoarthrosis (20 cases), or the disappearance of the epidural fat (10 cases). These lesions, sometimes associated and stackable to those objectified by imaging, justified in all cases a laminectomy or hemilaminectomy, associated depending on the case to a disectomy, a foraminotomy, an abrasion of the articular masses, or to ablation of the yellow ligament. Lumbar or lumbosacral fusion was performed in 15 patients.

Myelography helped discover herniated disk in four of the 30 patients who were operated on it; in the other 26, diagnosis was based on the scan. The hernia has affected L4L5 disc in 18 patients, L5S1 disc in seven patients, and both in the five other patients. It was calcified and excluded at L5S1 in a patient, and excluded subligamentous in 14 patients. The demographic profile of patients with excluded and/or sub-ligamentous herniated disc was similar to that of patients with an unusual herniated disk. The intervention consisted in all cases of a disectomy. The female patient with calcified L5S1 herniated disk showed no semiological peculiarity: aged 40 years, she suffered for two months from a mechanical nerve root pain responsible of a walking limitation less than 100 meters. Apart from the spinal syndrome, the assessment has objectified Lasegue at 60°, and hypesthesia to tact in the territory of S1. The scan did not objectify anomaly of L3L4, L4L5 and L5S1 interbody spaces. Myelography highlighted amputation of the right S1 root. Calcification of the hernia was discovered by operation.

The evaluation of the results of surgical treatment includes both patients with LSS and those with herniated disk. The results were good or satisfactory in 70 of the 72 patients with LSS, and in 29 of the 30 patients with herniated disk. Satisfaction consisted of complete or near-complete disappearance of the nerve root pain, net regression of low back pain and improvement in the walking distance compatible with the activities of daily life. Forty of the 102 patients (39%) suffered from low back pain requiring the use of analgesics. Twenty patients including 10 of the 15 who underwent fusion wear a waist belt.

Two patients with a CLR were re-operated on. The first case was a woman, company director who was then 30 years old having a lumbar nerve root pain related to a herniated disk, subject to laser treatment in Poitiers. This treatment resulted in failure leading to reoperation ten years later: the female patient was suffering from bilateral claudicant lumbar nerve root pain confining her almost completely to bed, and associated with paresthesia and sphincter disturbances. MRI revealed herniated disk in L4L5 and L5S1, associated with an L4 grade I anterolisthesis. The reoperation consisted of a double disectomy and an L4-sacrum fusion. The exact evaluation of the reoperation performed twelve years ago is this difficult today because of the coexistence of a major depressive syndrome. The second patient with LSS and subject to revision surgery was a 60 years old bank executive whose first operation, consisting of a laminectomy, was followed by a notable decrease of low back pain and nerve root pain. A fall due to a slip which occurred three months after the first operation resulted in the return of the lumbar nerve root pain. An MRI revealed L4L5 herniated disk subject to disectomy. A patient operated on for a herniated disk had postoperative after effects marked by spondylodiscitis. The failure of antibiotic treatment underpinned by the assumption of a banal germ led to the initiation of TB treatment. This resulted in retrobulbar neuritis attributable to Ethambutol.

Discussion

Our study included 102 cases of patients operated for a LSS or a herniated disk. The rosary picture at myelography and/or scan and/or MRI was characteristic of the LSS. The same tests contributed to the diagnosis of herniated disk. Brevity or thickening of blades, degenerative disc diseases, hypertrophy of yellow ligament and posterior inter-apophysis osteoarthrosis were the lesions responsible for the lumbar canal stenosis in our patients suffering from LSS. The intervention consisted in actions to stop these lesions. Fifteen patients with a lysthesis were subject to fusion. Herniated disk affected mostly L4L5 and L5S1 discs and required a disectomy in all cases. The results of this surgical treatment were satisfactory in 99 of 102 patients operated with an average duration of more than eight-year follow-up. The results were characterized by the complete or near-complete disappearance of the nerve root pain, notable improvement in the walking distance, regression of low back pain, and resumption of activities. The limitations of our study should be taken into account for a relevant measure of its results. We excluded patients that we could not be able to contact to proceed to the evaluation of treatment, and patients whose operation report was without a detailed description of the anatomical lesions. In addition, the cases which underwent surgery only represent a small proportion of our patients with herniated disk or LSS justiciable of a surgical treatment, which cost is not affordable with the majority of our patients. This cost justifies the small proportion of
patients operated for conditions whose frequency and impact have been reported in an earlier study conducted in the department. It also justifies the small proportion of women operated for LSS, a condition that seems to touch with predilection obese women aged about 50 years.43 The results of our study agree with the main data from literature, both anatomically and therapeutically.

From the anatomical point of view, the two diseases have no special feature: the anatomical aspects of lumbar spinal stenosis and herniated disk of the black Africans are similar to those of the Caucasian and the Asian. Herniated disk affected with predilection levels L4-L5 and L5-S1, location of lumbar herniated disk in 80-90% of cases. Lumbar spinal stenosis featured both congenital aspect and acquired aspect. Like other authors, we found that the boundary between the two nosologic entities that are herniated disk and lumbar spinal stenosis is sometimes blur, a Claudican herniated disk that may be responsible of symptoms similar to that of LSS. Lesions found in our patients (disc attack, posterior inter-apophysis osteoarthritis, hypertrophy of yellow ligament) are similar to those reported in the literature. Thus, in a general journal on the different aspects of LSS, Issack et al11 have established the role of degenerative factors in lumbar canal stenosis. The lesions mainly touch the intervertebral disc, the posterior joints and soft elements, including the yellow ligament. The long-term effect is more significant with the surgical treatment than the medical treatment.

The results of surgical treatment of our patients are in perfect agreement with the literature data. The evaluation of treatment performed in our patients after an average of more than eight years, showed a high satisfaction rate, only two patients with LSS were re-operated. Our results are in harmony with those from the study of Kaymaz et al2 who demonstrated the beneficial effect of simple posterior decompression by laminectomy, after an evaluation at 6 and 12 months of 80 operated patients. The beneficial effect of surgical treatment applies to nerve root pain as well as low back pain. This is evidenced by the recent prospective study of Jones et al13 of 119 cases of LSS who underwent laminectomy. This study reported a significant regression of low back pain after an evaluation at six weeks and at one year. The outcome of surgery for LSS seems furthermore independent of race: thus, Lad et al14 after a comparative study between black and white Americans having undergone laminectomy for LSS for at least two years did not find a higher risk of reoperation in blacks. There is, contrast, among blacks a higher risk of post-operative complications, as well as higher hospital duration and costs. One of our patients, a woman, was subject of reoperation after a laser treatment. Her case recalls the results of the study conducted by Cheng et al15 who found a higher risk of reoperation after noninvasive discectomy by endoscopy.

References

Clinical presentation of patients with adult onset Still’s disease in Nairobi: case series

Otieno FO, Oyoo GO, Otieno CF, Omondi EA

Abstract

Introduction: Adult Still’s Disease (ASD) is a systemic inflammatory disorder of unknown etiology, typically characterized by a clinical triad (daily spiking high fevers, evanescent rash, arthritis), and a biological triad (hyperferritinemia, hyperleukocytosis with neutrophilia and abnormal liver function test).

Objective: This case series set out to describe the clinical characteristics of patients with ASD seen at a rheumatology clinic in Nairobi.

Results: After a record search, 8 patients were noted to have ASD. Fever and arthritis were noted to be most predominant presenting features with almost all the patients having hyperferritinemia.

Introduction

Adult Still’s Disease (ASD) is a rare disorder, known to exist world-wide, with equal distribution between sexes, and with three quarters of the patients reporting disease onset between 16 and 35 years of age. When starting before 16 years old, Still’s disease is called Systemic-Onset Juvenile Idiopathic Arthritis (SOJIA), classified within the spectrum of juvenile idiopathic arthritis. No single cause for ASD has been identified, although a variety of infectious triggers and genetic factors have been suggested.

There are several epidemiological studies on ASD from around the world. A retrospective study of 62 patients from France estimated the incidence of ASD at 0.16 per 100,000 persons, with a bimodal peak at ages 15-25 and 36-46, and equal distribution between the sexes. A retrospective study of 45 patients from the Netherlands reported a median age of onset of 25 years (range 16 to 65 years) with 27% presenting over the age of 35, and 60% women. An epidemiological survey from Japan estimated the incidence among men at 0.22 per 100,000, and among women at 0.34 per 100,000, with a mean age of 38.1 years, 67% presenting over the age of 35, and 65-70% women. However, several cases with onset of ASD after the age of 60 have been reported.

The initial symptom of ASD is usually sudden onset of daily spiking high fever. Fevers typically peak once daily, in the late afternoon or early evening, generally exceeding 39°C and lasting under 4 hours, returning to normal in 80% of patients even without antipyretic treatment. Fever sometimes has a double quotidian pattern, with highest spikes occurring in the late afternoon or early evening. Overall incidence of fever in ASD across the largest retrospective studies is 96%. The classic rash in ASD is an evanescent salmon-pink, macular or maculopapular eruption, predominantly involving proximal limbs and trunk, which usually emerges with the fever, especially in the evenings. The rash can exhibit the Koebner phenomenon, and as a result may occur especially in areas subject to friction, i.e. tight clothing. The rash may be mildly pruritic, and is often confused with drug allergy. Histology shows mild perivascular inflammation of the superficial dermis, with primarily lymphocytes, histiocytes, and dermal edema. Immunohistochemistry may show C3 deposition in the blood vessel walls. Overall incidence of rash in ASD is 73%.

Musculoskeletal symptoms are found in the majority of patients with ASD. Arthritis may initially be mild, oligoarticular and transient, evolving over a period of several months into a more severe, destructive, symmetrical and polyarticular form. Most commonly affected joints are knees, wrists and ankles, although elbows, shoulders, hips, interphalangeal, metacarpophalangeal, metatarsophalangeal, and temporomandibular joints may also be involved. Progressive changes in the wrist joint, with precipitate or carpometacarpal joint space narrowing, typically present 6 months after disease onset and may develop to ankylosis in 1.5 to 3 years. Incidence of arthritis in ASD ranges from 64% to 100%.

Generalized myalgias, often coinciding with fever spikes are also found in the majority of patients. Myalgia may be severe and debilitating. Inflammatory myopathy is rarely found in ASD, but serum creatinine kinase and aldolase...
concentrations can be slightly elevated. Incidence of myalgias in ASD ranges from 56% to 84%. ASD has been associated with marked elevations in serum ferritin concentration in approximately 70% of patients. Serum ferritin concentrations are usually higher in ASD than in other inflammatory conditions.

Case presentations

A total of 8 patients with ASD were identified after a record search of all patients at Nairobi rheumatology clinic. Their demographic and treatment variables were ascertained and are summarized in the Table 1.

Table 1: Demographic treatment and variables of the patients

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
<th>Patient 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39</td>
<td>48</td>
<td>32</td>
<td>37</td>
<td>37</td>
<td>24</td>
<td>45</td>
</tr>
<tr>
<td>Gender M/F</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Fever Y/N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Arthritis Y/N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Myalgia Y/N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Others (specify)</td>
<td>Splenomegally</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin levels H/L</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>WBC H/N/L</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>H</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Neutrophils H/L/N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>H</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>LFTs N/AbN</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>ABN</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>ESR N/H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>CRP N/H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>RF P/N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>ANA P/N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

The age at presentation was between 21 to 48 years, with mean age of 35.4 years. There were 5 male patients. Fever and arthritis were the predominant clinical features with 7 out of 8 patients presenting with either features. One patient was noted to have splenomegally.

Laboratory parameters: Hyperferritinemia was seen in 7 patients. Only 1 patient had a high white blood cell and neutrophil count. Abnormality in liver function test was seen in 1 patient. A high acute phase response was seen in 6 patients, with 5 patients having elevated ESR, 3 with high CRP levels and 2 with elevations of both CRP and ESR. Where ANA and RF testing was available, the results were negative.

Discussion

This evaluation set out to review the clinical presentation of patients diagnosed with ASD based on the EULAR diagnostic criteria. Eight patients were noted to have ASD, after a record search of all patients attending rheumatology clinic in Nairobi. All the 8 patients had their clinical features reviewed in this evaluation. The mean age at presentation of the patients was 35.4 years, with an age range of 21 to 48 years. Five patients were male. These findings are consistent with several epidemiological studies on ASD from around the world. In the largest case series report from Africa, Cheikhrouhou Abdelmoula et al., studied 11 cases of patients with ASD with a similar mean age of 35.4 years.
Conclusion

ASD is a rare disease in our local set up, but with more aggressive suspicion index and appropriate investigations more cases can be identified.

References

Juvenile angio-Beḥçet’s disease: report and brain MRI findings of 3 cases

Lefkir S1, Slimani S2, Brahimi N1, Bekour D1, Rahal F1, Ladjouze-Rezig A1

Abstract

Background: Beḥçet’s Disease (BD) is a vasculitis of unknown origin; it is characterized by recurrent mouth and genital ulcerations, uveitis and diverse systemic manifestations. It is very rare in children. Vascular tropism is mainly characterized by phlebothrombosis; arterial involvement is less frequent.

Case presentations: We report here three cases of juvenile angio-Beḥçet in two boys aged 11 and 16 years-old and a 14 year-old girl. All three children were admitted for a newly-diagnosed BD characterized by multiple, migrating and recurring phlebothromboses, treated with anticoagulants and corticosteroids and requiring cyclophosphamide pulses, along with a severe uveitis in one patient, having required the addition of azathioprine, with favorable outcome. Complications such as pulmonary embolism and Budd-Chiari syndrome were present in case 3, which improved under immunosuppressants. In order to prevent future thrombosis, anticoagulants were maintained for long periods as well as immunosuppressants. Magnetic Resonance Imaging (MRI) of the brain revealed subclinical findings in the 3 cases.

Conclusions: Development of venous thrombosis in juvenile BD cases should not be overlooked and special attention is required for these cases in order to improve their disease outcome. Performing advanced radiologic investigations is useful to detect subclinical cases and delineate the extent of affection. Prognosis remains variable but often bad, depending on the presence of vascular, ocular and neurological complications.

Keywords: Juvenile angio-Beḥçet, Phlebothrombosis, MRI brain, Rare disease, Immunosuppressants

Introduction

Beḥçet Disease (BD) is a vasculitis of unknown origin. It is a chronic, complex multisystem disease characterized clinically by oral aphthae, genital aphthae, cutaneous lesions, and ophthalmic, neurologic, or rheumatologic manifestations. The first description of Beḥçet’s disease was probably by Hippocrates in the fifth century BC1, and the first modern account was presented in 1937 by the Turkish dermatologist Hulusi Beḥçet, who reported on a patient with recurrent oral and genital aphthae and uveitis2.

It is rare in children. Arterial and venous vessels can be involved, with phlebothrombosis as the main vascular manifestation, arterial involvement being less frequent3.

New criteria for BD4 are represented by mouth ulcerations (1 point, compulsory criterion), genital ulcerations (2 points), cutaneous lesions (1 point), ocular involvement (2 points) and a positive pathergy reaction (1 point); diagnosis is made when 3 or more criteria are present. There is no specific criteria, either clinical, laboratory or histological, for the diagnosis. We report here three cases of juvenile angio-Beḥçet.

Case 1

D. Mourad, aged 16 years was admitted to the Department of Rheumatology, Ben Aknoun Hospital for the management of a Behçet disease evolving since he was 12 years, with multiple deep and recurrent phlebothromboses, having affected the sural veins, the right brachiocephalic vein, the lateral sinus on the brain Magnetic Resonance Imaging (MRI) (Figure 1), associated with bucogenital ulcerations and posterior uveitis. Clinical examination revealed a small stature, truncal and facial obesity (cushingoid aspect), mouth ulcerations, a swollen left leg, negative for Homans’ sign, collateral venous circulation on the chest (Figure 2) and skin lesions, mainly represented by cicatrized pseudo-folliculitis. Laboratory findings: Erythrocyte Sedimentation Rate (ESR) 45mm, C-Reactive Protein (CRP) 12 mg/L, high White Blood Cells (WBCs) count (17,100/mm3), positive antiphospholipid antibodies. Ophthalmologic evaluation has shown posterior uveitis of the left eye. The patient was treated with anticoagulants.
and glucocorticoid pulses, followed by monthly pulses of cyclophosphamide for 6 months (500 mg/m²) and colchicine (1 mg/day). Evolution was characterized by stabilization and improvement of skin lesions as well as of antiphospholipid antibodies (APL); however, two episodes of uveitis have been noted, improved later by azathioprine and glucocorticoids (0.6 mg/kg/day).

**Figure 1:** Brain MRI angiography of case 1: Thromboses of the sagittal and lateral sinus (arrows on the left image)

**Figure 2:** Collateral venous circulation on the chest wall of case 1

**Case 2**

An 11 year old boy, presenting with a history of recurrent sural and femoral phlebothromboses, at the age of 8 and 9 years, treated with anti-vitamin K, presented with bilateral panuveitis, mouth ulcerations as well as erythema of the upper and lower limbs and poor general condition. At admission, the child was pale, wasting (BMI 11kg/m²), with arthralgia of the large joints. Clinical examination found spinal stiffness, pain on the left clavicle, and stiffness of both shoulders and a limitation in the opening of the oral cavity, with glossitis. Skin examination revealed erythema nodosum on the dorsal side of the left MCP 1. Ophthalmological examination revealed right side blindness. Laboratory findings revealed hypochromic anaemia (7.7g/dL), high (WBC) count (leucocytosis) (19,700 /mm³), thrombocytosis (745,000/mm³), elevated ESR (80 mm/1st hour) and high CRP at 231 mg/L. There was also low serum albumin (24 g/L) and positive antiphospholipid antibodies (IgM anticardiolipin). Cervical ultrasonography found a thickening of the left carotid artery and the left jugular vein, associated with cervical and sub-mandibular lymphadenopathy. Brain MRI revealed cortical and cerebellar atrophy and zones of demyelinization of the white substance (Figure 3), testifying vasculitis. The patient was treated with colchicine (1 mg/day), aspirine (100mg/day), methylprednisolone (4 mg/day) along with 6 courses of cyclophosphamide (500mg/m²) and calcium/vitamin D supplementation. Six months later, the patient was well, and gained 4 kg of weight.

**Figure 3:** Brain MRI of case 2: Multiple nodular lesions of the periventricular white substance

**Case 3**

A young girl aged 14 years was admitted to the Department of Rheumatology, Ben Aknoun Hospital for angio-Beḥçet beginning at the age of 12 years, with inflammatory arthralgia and recurrent buco-genital ulcerations. One year later, appearance of headache, unhalted with analgesics, followed by phlebothrombosis of the left lower leg and then by a massive pulmonary embolism, treated with anticoagulants. Clinical examination noted lingual ulcerations, a positive pathergy reaction, an abdominal collateral venous circulation (Figure 4), as well as painful knees and ankles. Laboratory findings revealed normal values for ESR, complete blood count, rheumatoid factor, Anti-Nuclear Antibodies (ANA), Anti-Neutrophil Cytoplasmic Antibodies (ANCA) and APL antibodies. Brain MRI revealed multiple thromboses of the sagittal and the right lateral sinus (Figure 5).
Discussion

Behçet’s disease is rare in children and often under-diagnosed. It may be severe, and be responsible for vascular involvement, mainly venous thrombosis, associated with the presence of antiphospholipid antibodies, like in cases 1 and 2. Clinical presentation in children seems as rich and variable as in adults; however, some particularities have been noted, such as an equal involvement of boys and girls, a more frequent bowel and vascular involvement. Like in adults, there are no pathognomonic laboratory findings. The Phlebothrombosis seems frequently associated with cutaneous manifestations such as erythema nodosum, pseudo-folliculitis and uveitis. Phlebothromboses are mainly seen on lower limbs. Arterial involvement is rare, as was seen in case 3. It is more easily diagnosed nowadays thanks to modern imaging techniques. Budd-Chiari syndrome is rare and severe; it was seen in case 3; its frequency seems very low (< 1%). The diagnosis of Behçet disease is difficult in children because of the delay between the first symptoms and the complete presentation, allowing diagnosis.

In order to prevent future development of thrombosis, anticoagulants should be maintained for long periods, associated with immunosuppressants, in order to reduce systemic inflammation which is responsible for the endothelial activation. Prognosis is still severe, depending on the evolution of the vascular, ophthalmological and neurological involvement, which seems more severe than in adults. An aggressive management may limit the consequences.

Behçet’s disease is under-diagnosed in children and vascular involvement is a life threatening condition that should be seriously considered. It could be concluded that subclinical vascular involvement is overlooked in juvenile BD patients and performing advanced radiologic investigations is useful to delineate the extent of affection. In order to avoid the development of thrombosis, anticoagulants are maintained, associated with immunosuppressants.

Conflicts of interest: The authors have no conflict of interest to declare.

References


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The *African Journal of Rheumatology* is published biannually by the The African League of Associations for Rheumatology (AFLAR). The journal aims to publish papers on basic and clinical research in rheumatism and arthritis and be a vessel of sharing knowledge a close the globe. Original research work, reviews, case reports and other relevant scientific work will be published in the journal on the understanding that the work submitted will not be under consideration in any other journal. This must be stated by the authors when submitting papers.

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2. 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.

3. References should be numbered in order of appearance (Vancouver style) and only those cited should appear in the reference list.
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- Post Graduate Diploma in Hospital Management

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