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Rheumatoid arthritis in Kenya

Otieno FO1, Moots RJ2, Oyoo GO1

Rheumatoid Arthritis (RA) is a systemic autoimmune inflammatory disease characterized by persistent synovitis and progressive destruction of cartilage and bone. It is associated with progressive joint damage, pain, fatigue, and disability, as well as the elevation of acute-phase reactants such as C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR)1-2. It is a common disease, affecting about 1% of adults aged 35 years and 2% of adults aged 60 years in the United States1. Similar prevalence figures have been reported worldwide2.

In the past, rheumatoid arthritis was considered rare in Africa and not an important cause of admission to hospital in African patients. Indeed, a case of RA in Kenya in 1962 was considered rare enough to warrant a publication3. However, in 1979, Bagg et al4 described 76 patients with RA over an 18 month period, showing either increasing recognition or an increase in the number of patients with that diagnosis. Bagg et al4 observed that age, sex ratio and pattern of joint involvement resembled that seen in Europe and USA.

The prevalence of rheumatoid arthritis in Kenya remains unknown today, as there have been no population studies. Recent hospital studies suggest an increasing prevalence and/or incidence of RA among Kenyans, with male to female ratios ranging from 1:6 to 1:105-9, an observation that is pretty much consistent with studies from the West and from other African countries5-9. The mean age at presentation ranges from 43.5 years to 48 years5-9.

The few published studies of RA in Kenya have endeavored to describe presenting features in these patients. These include: serologic profile, pulmonary manifestations, haematological complications and cardiovascular risk profile.

Pulmonary manifestations appear to be especially prevalent in Kenyan patients with RA. In an assessment of 166 ambulatory RA patients attending clinic in Nairobi, using spirometry, Biomdo et al6 found pulmonary abnormalities in 38.5% of RA patients documented pulmonary pathologies. The predominant pattern was obstructive at 53% of all the abnormal lung functions, with a restrictive pattern in 44%. The study however found most of the manifestations to be mild. This study established that occurrence of pulmonary complications, typically mild, correlated with older age, respiratory symptoms and severe disease activity.

Several studies in the West have shown RA to be an independent cardiovascular disease risk factor. In Kenya, Kirui et al7 reported a case control study that compared the presence of ‘traditional’ cardiovascular risk factors between an aged and sex matched cohort of patients without RA and those with RA in Nairobi. They observed a statistically significant increased occurrence of hypertension among RA patients 41.3% in comparison to the ‘normal’ population 22.5%. Use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) and steroids as would be expected, was shown to be associated with presence of hypertension in this study. Presence of other traditional cardiovascular risk factors i.e. diabetes, dyslipidemia, smoking and obesity was observed in both groups with no significant difference. The study noted clustering of risk factors among patients, with no significant association of the risk factors, suggesting additional mechanisms responsible for cardiovascular disease among the RA patients.

Treatment of RA has improved dramatically over the years. However there are still no local treatment guidelines to guide the management of RA patients in Kenya and other sub-Saharan countries. Local rheumatologists therefore have to rely on international guidelines to manage patients. As there are limited investigational modalities, some of which may be high cost, investigating patients appropriately is challenging and may be expensive. There is therefore an urgent need to develop relevant treatment guidelines to support effective management of RA in Kenya. Lobby and advocacy with relevant authorities must be scaled up to ensure the availability of affordable medicines and investigations for our patients with RA. One reassuring finding from Kenyan studies is that, despite the challenge of health care...
financing, most patients seen in clinic with RA are taking disease modifying drugs. Biomdo et al, while looking at pulmonary abnormalities in 166 patients with rheumatoid arthritis in various rheumatology clinics in Nairobi, noted that 78% of the patients were on DMARDS. Kirui et al found 80% of patients at Kenyatta National Hospital with RA took DMARDS. Mbuthia et al sampled 104 RA patients at Kenyatta National Hospital, where 75% were on DMARDS. Steroid use also varied with various studies, showing 21.7% - 57% of all patients taking these drugs.

Whilst low-cost DMARDs are now widely used in major Kenyan centres, the uptake of biologic DMARDs remains low, as in other developing nations, due to the high cost of these drugs. A number of biologic agents have been registered for use in Kenya for RA. In the only publication of biologic DMARD use to date, Oyoo et al recently reported outcomes of 41 patients treated with rituximab after failing conventional DMARDs. The evaluation noted significant improvement in both disease activity and functional status of patients at 6 months of follow-up after receiving rituximab. In order to document outcomes with other biologic agents, a registry of each biologic would be useful to understand real life outcomes.

Whereas great strides have been undertaken to report various aspects of RA in Kenya, much further work remains, to establish the burden of this disease in the general population. Population wide epidemiological studies will be useful to understand the burden of disease. Other perspectives of diseases remain to be clearly understood, e.g population-specific determinants of disease (onset, severity and progression), prognostic factors, determinants of treatment response. Operational research will be key in determining more cost effective approaches to providing care and treatment to the rising number of patients, in the midst of scarce resources. In order to address this challenges, support from key stakeholders will be vital; the Ministry of Health and other governmental authorities need to provide support and leadership.

In the background of the myriad of challenges faced in the management of RA in Kenya, the various stakeholders: Arthrheuma Society of Kenya, the local rheumatologists, industry partners, government and non-governmental partners, deserve praise for a job well done to alleviate the suffering of patients. One should however note that these efforts are only the start of a much longer yet exciting journey.

**Key words:** Rheumatoid Arthritis (RA), Disease Modifying Anti Rheumatic Drugs (DMARDS), Non-Steroidal Anti-Inflammatory Drugs (NSAIDS), Steroids

**References**

Bioethical challenges to rheumatology in resource poor areas: a review

Meltzer M¹, Price A²

Abstract

Objective: To outline the bioethical challenges specific to rheumatology in resource poor areas.

Data source: Published articles and selected personal communications on bioethical challenges and education in rheumatology.

Study design: A narrative commentary.

Data extraction: Online searches using PubMed and Google Scholar and personal experiences (Michele Meltzer, Amy Price).

Conclusion: Autonomy emphasizes respect for the individual and self-determination. We discuss how this can be dealt with because of lack of medical literacy. Moreover, conflict of interest should be revealed to the patient. Beneficence includes affirmative steps to improve public health and the role rheumatologists can play in advocating for increased public education and access to care for their patients. Nonmaleficence, encompasses the premise of doing no harm. Physicians need to be competent, but many parts of the world lack trained rheumatologists to teach the special skills required to diagnose and treat not only complex musculoskeletal disease but also chronic multifaceted pain conditions. Finally, we consider justice when fair allocation of scarce resources is difficult. Among other choices related to justice, physicians must decide how to allocate their time because of scarcity.

Introduction

A recognition of bioethical challenges faced by rheumatologists is important to develop a framework to manage or solve particular issues. In a 2013 survey, U.S. rheumatologists identified conflict of interest, the cost of modern treatment (to patients as well as to society), and a perceived deficit in ethics training among medical professionals, among other ethical challenges in rheumatology¹.

These challenges exist everywhere, to varying degrees depending on the economic, political and cultural situations within a given geographical region, but particularly in low- and Limited-Income Countries (LLICs).

This paper will discuss particular bioethical challenges within LLICs for rheumatologists and their patients. The four basic and well-known principles of bioethics will be used to guide the discussion: autonomy, beneficence, nonmaleficence, and justice². We note that one complication is the international lack of research and methodology manuscripts that are culturally and resource specific to practitioners in low-income settings. Clinicians are ill-equipped and struggle to give appropriate care when access to medicines, devices, supportive care, and consultants are limited. It can be challenging for each rheumatologist to decide what part he or she shares in the burden and/or responsibility for health “equity” so that everyone has fair opportunity for health within the medical system³.

Case study

We begin by exploring the following case example. A caring father brings his six-year-old son to a rheumatology clinic in Nairobi. The child has severe destructive juvenile idiopathic arthritis and cannot walk or even feed himself because of the deformities. Two years earlier, the father had taken the boy to a rheumatology clinic, and he was started on methotrexate and prednisone. But the father did not return because it was an eight-hour bus ride to attend clinic and he could not afford the bus ride nor the time missed from work. The father did not understand how sick his son was and the consequences of not taking medication.

Now, there is permanent damage to the boy’s joints and the boy will never be able to live independently. The medical team decides to admit the boy for the...
management of his rheumatoid arthritis, however due to resource limitations they are only able to administer corticosteroids. The medical team felt helpless and just wanted to do something. The lack of resources and training caused them to overlook the fact that hospitalization was unwarranted as the patient could receive corticosteroids as an outpatient. They were despondent that once again the medical system failed a vulnerable child. One could argue that the hospital admission is just more money wasted and the toxicity from the prednisone will just compound the suffering. The treating physicians are stuck at what to do next. There are no rehab facilities for children and orthopaedic surgery would be too expensive and very complicated.

Foundational principle of bioethics: Autonomy

As one of the foundational principles of bioethics, autonomy emphasizes respect for the individual and self-determination. This concept involves having the authority to make decisions for oneself, having sufficient information in order to make an informed decision, and having one’s own choices be respected by others. But this concept is complicated by the fact that many parts of the world embrace a value system that places the family, the community, or the society as a whole above the individual person. The individual patient should have the right to decide if he or she wants to delegate decision-making authority over personal care to a surrogate, such as a family member. The challenge facing bioethics in a resource-poor setting is not to mislead people with unrealistic promises of autonomy that very few communities can achieve, but to articulate moral principles and societal values that promote equitable access to care and broaden the goals of medicine and public health.

The opening case highlights a few of the bioethical challenges to autonomy. The father delayed follow-up treatment, either due to ignorance about the particular illness or to the high cost of care. As a result, the child presented to the clinic too late to benefit significantly from treatment. But, as we will discuss, the medical staff may not have had the resources to fully inform the father about his son’s disease. Another issue is that there are alternative practitioners of medicine in many LLICs. It is not uncommon for people with less education to seek care from these alternative practitioners, who often encourage the patient to discontinue conventional therapy. The combination of an absence of a referral system, a lack of insurance, and a limited understanding of the disease created delay in seeking appropriate care.

In order to effectively participate in the decision-making process, the patient must be informed about his or her disease process in vernacular that is readily understandable. The need to improve medical literacy is a global problem. Many rheumatic diseases are complex, and every effort should be made to ensure the patient understands the medical condition and treatment options. Even when the patient recognizes the need to seek treatment, this acknowledgement may be insufficient in areas of severe poverty and pose further ethical challenges that are less common in more developed countries. For many patients, spending time in the hospital means a loss of earnings and puts the family’s economic well-being in jeopardy.

Informed consent and literacy: Low levels of education, literacy, and health literacy, which are associated with poor health, can make even informed consent a challenge. However, prior to any procedure or research, the patient should give informed consent. When seeking the consent of a financially stressed patient to participate in a research study in exchange for remuneration, care must be taken so that the arrangement is not coercive. Each research candidate should receive adequate disclosure of potential risks and unknowns involved with the study, as well as information about other treatment alternatives that are more established. Documentation of responsibility for adverse events should be made available. Moreover, the definition of adverse event, and the length of time from the start of treatment to adverse event, needs to be part of the informed consent process.

Informed consent also requires that the physician discloses any conflict of interest. Many countries recognize the influence on physicians from perks and financial payments provided by pharmaceutical companies, and have implemented restrictions on such activities as well as public reporting requirements. These interactions can bias a prescriber’s choice of medication in favour of more expensive drugs with no clinical evidence showing that they are more effective than less costly drugs. In the United States, patients can now access a public website to view legally required disclosures of income and other financial benefits received by healthcare professionals from pharmaceutical and medical device companies. All over the world pharmaceutical companies have a history of providing stipends to attend conferences, deliver training and for Continuing Medical Education (CME). Research has found this influences prescribing habits regardless of the efficacy of the intervention.

External considerations in autonomy: In low income countries clinicians face increasing pressure in the struggle to provide for their families and their patients. For example, when the clinician wants to send their own children to university or pay for a relative’s ongoing medical care those stipends carefully saved can make the difference between meeting the need or seeing the family need left unmet. There is a real concern that over time this may unconsciously influence how the doctor makes a choice about what to provide in terms of prescriptive
interventions. The information about potential conflict of interest and how this could occur might be disseminated within the community and should be shared with the patient and the clinician. By the same token, medical students must also be alerted to the potential conflict posed by receiving financial benefits and gifts from pharmaceutical companies.

**Privacy and confidentiality:** Finally, medical confidentiality is one of the cornerstones of respect for patient autonomy. Patients need to know that what they discuss with the healthcare professional is private. If not, they will be reluctant to reveal sexual history, diseases that could affect employment, and mental health. When author, Michele Meltzer (MM) served as a visiting consultant in Africa and India in 2011 to 2015, privacy was almost non-existent. Often more than one patient at a time was in the exam room, and in the hospital wards, curtains were either not available or not drawn when the patients were interacting with medical staff, and of course, curtains do not block sound. Further complicating the issue of privacy, many patients MM saw in both Kenya and India carried their medical records with them. As LLICs develop electronic medical records, policies on medical record access and security will evolve

**Foundational principle of bioethics: Beneficence**

The principle of beneficence includes public health and taking affirmative steps to enhance it. In many areas of the world, treatment for rheumatic diseases is not available, and accommodations are insufficient for people with disabilities. For instance, in most of sub-Saharan Africa, musculoskeletal health has been almost completely neglected principally due to fierce competition for scarce resources. It is common for public health to take priority and this means that resources are directed towards infectious disease and maternal care. A disease that does not spread is given lower priority even though an infection may last only a few days while a chronic or non-infectious disease may last a lifetime. Rheumatologists and their patients need to educate policymakers and non-profit organizations about the incredible burden, including years lost to disability, and inability to contribute to the workplace that rheumatic diseases create for individual patients and for society. Epidemiology studies on the prevalence and impact of rheumatic diseases would be of great value to raise awareness, prepare families and to advocate for care.

**Peer to peer resources:** Consider systemic lupus, an autoimmune disease with variable manifestations. Rheumatologists are in a position to improve patient education about the disease. When one of our authors Michele Meltzer (MM) attended two meetings of the Lupus Support Group in Nairobi in 2012 and 2013, she met people who were eager to learn more about their disease and enjoyed the camaraderie from meeting others with similar diseases. Another author Amy Price (AP) found the same in her trips to these nations and was impressed with the willingness of the sick to attend to and comfort each other. It has been observed that even the elderly are willing to learn electronic communications skills so they could form communities of learning around the disease. Many felt socially isolated by having a disease no one seemed to have ever heard about. They knew little about their disease and lacked personal resources to find more information. These patients would benefit from knowing that medications are available that may help. Support groups are in a position to advocate for the availability of these drugs and also for the rights of those disabled by the disease and their families. Although more work needs to be done, both authors found such support groups can reduce psychosocial factors and improve disease self-efficacy and quality of life, especially in areas where the physicians have a large patient load.

**Foundational principle of bioethics: Nonmaleficence**

**Access to knowledge:** The principle of nonmaleficence encompasses the premise of doing no harm. Physicians must be competent, having not only a wealth of technical knowledge but also an understanding of how to manage the complexities of chronic disease within their own communities. Achieving this competence in rheumatology is challenging because there is a worldwide shortage of rheumatologists. For example, Canada suffers from a shortage of rheumatologists and is actively exploring ways to make rheumatology more attractive to students. The shortage of rheumatologists is especially severe in LLICs. As a result, the many medical schools in Africa will have an insufficient number of instructors in rheumatology, which in turn will likely result in fewer graduates entering the rheumatology field and a general deficiency in the basic understanding of rheumatic diseases. In 2005, there were 4,946 adult rheumatologists and 218 paediatric rheumatologists in the United States. Meanwhile in sub-Saharan Africa (excluding South Africa), less than twenty rheumatologists are available to serve about 800 million people. Physicians do not work in a vacuum. Trained nurses, physiotherapists, occupational therapists, to name a few, are part of the professional team that lack the specialist training for the treatment of musculoskeletal disorders. There are too few specialists to treat patients and train staff compounded by the added challenge of lower healthcare professional training standards. These diseases require specialized care and an inaccurate diagnosis can do great harm. For example, a young man with back pain due to ankylosing spondylitis might be diagnosed and treated for degenerative disc disease. In the meantime, he
develops irreversible changes in his spine. Or a young woman comes in with joint pain. No one has the skill to question her further and find that she has symptoms of systemic lupus and in fact her most serious problem is her kidneys are failing.

Access to care: But knowledge is not the only important factor in nonmaleficence. Students also require tools to analyze and understand major ethical issues, such as drug and medical device counterfeiting and the quest for profit. Scarcity of resources also requires physicians to make difficult choices about intensive care, access to surgery, and use of medications, as documented in a survey of Ethiopian physicians. Problems of resource scarcity in many LLICs are compounded by political instability, corruption, and severe income inequality. Even something as basic as reliable electrical supply restricts availability of medications which require refrigeration.

The role of advocacy: In the United States, the American College of Rheumatology provides practice guidelines, educational material for both physicians and patients, and advocacy in the government. In all nations the influence of pharmaceutical companies can influence selection of drugs by doctors. The costs may be higher and efficacy lower for advertised, drugs. When specialist education is absent and medical journals are unavailable due to lack of access, the medical staff may look to a pharmaceutical representative for advice on how to treat patients. The inducement by gifts, trips to conferences and personal incentives is currently not under tight regulation in LLIC nations and this has the potential to influence the choice of drugs prescribed by the treating professional. More work is needed to elucidate the magnitude of this problem and then make physicians and healthcare professionals in LLICs aware. They can then create similar professional organizations in order to develop their own practice guidelines, educational materials, and advocacy committees. They are in a unique position to understand the difficult local challenges to patient care and could work together when confronted by difficult situations. Not only can these groups work with guideline developers to include information unique to their culture, they can negotiate with local officials to improve access to treatment and diagnostic studies. But most importantly, they can serve as a resource for individual physicians, health care workers to work together to make decisions about how best to deliver scarce care and provide emotional support to one another.

The biologics and newer medications now available for many conditions in rheumatology are extremely expensive and this means only those with sufficient financial means will benefit. Physicians should carefully consider alternative options to determine the most clinically effective and cost effective treatment. For example, triple therapy for treatment of rheumatoid arthritis (methotrexate, sulfasalazine, and hydroxychloroquine) treats rheumatoid arthritis effectively, and for a fraction of the cost of a biologic and may make the use of a biologic unnecessary. Furthermore, prior to ordering expensive tests and medications, physicians should consider the financial impact to the patient and his or her family. Although defacto rationing is part of daily life in LLICs, ethics committees or local physicians can create criteria for the fair use of various medications and tests. A good resource for physicians and patients is “Choosing Wisely.” Developed under the auspices of the American Board of Internal Medicine and Consumer Reports, Choosing Wisely lists diagnostic tests that are over utilized based on medical necessity, according to professional organizations that were asked to name the five most over utilized tests in their specialty of medicine. This excellent teaching tool increases awareness of these tests and decreases wasteful medical treatment and spending. The combination of community awareness, education, and fair use of medications may contribute to early and proper management and this could lead to better outcomes and increased quality of life for patients and the family members who care for them.

Managing corruption: Corruption is another problem that can reduce access to care. In Africa corruption was found to be a major barrier to patient access for cancer care. The health care systems, to varying degrees, were subject to bribery, extortion, and nepotism. Those with rheumatic illness are also vulnerable. Anti-corruption strategies, such as transparency and accountability, agreed codes of conduct, whistle-blower protection, and enhanced benefits for workers, could stave off corruption trends. Specialized Drug Shops (SDSs) provide distribution for most medications in sub-Saharan Africa. But medication distribution is another area that is poorly regulated. For example, only 12% of the SDSs in Kenya have refrigeration.

Foundational principle of bioethics: Justice

Allocation of resources is a major issue for all healthcare professionals, especially those with limited resources. Albert Jonson, medical ethicist and historian, has said that even artfully applied science, effective cures, and cost-effective care are morally deficient if such science reaches only some, if cures are unaccompanied by effective efforts at prevention, and if cost-effectiveness means limiting care to the elderly, the poor, chronically ill or the dying patient. John Stuart Mills, philosopher, when struggling with how to decide who is worthy of scarce resources, developed the theory of utilitarianism that advocated allocation so that the greatest number benefitted.

On an individual level, the rheumatologist is torn because of limited time to see patients. Even in the clinic, a decision must be made whether to see more patients in...
a cursory fashion or spend more time with fewer patients. Physicians need to care for family and extended family expenses as well as consider the schooling of their own offspring. It can be a difficult choice to work in the city where there is the support of peers and financial stability or in rural areas where there is little financial advantage or room for advancement. They struggle to balance the advantages of the more lucrative private system where conditions are better for those who can afford to pay or to meet the need of the population within the public system. Decisions for diagnoses and treatment are equally difficult. With limited funds how does one decide if a particular treatment or diagnostic test is worth the financial burden it will place on the patient and their family? And finally a nation’s health professionals will face the issues of how tribal identity, sex, and race will influence fair and equal access to health care.

Conclusions

Common challenges to the practice of rheumatology-conflict of interest, cost of therapy, deficits in bioethics training-are compounded in LLICs by limited income, political instability, war and corruption. The determinants of health are much more complex than in Western countries with competition between ethnic groups and volatile unstable economies.

As the number of rheumatologists in LLICs increases, education in bioethics is essential to understand the theories needed to create policies to improve the complex medical systems. The opening case illustrates various aspects of medical ethics discussed in this paper. The father did not understand the seriousness of his son’s disease. Medical access complicated the problem, and the treating physicians did not have the tools to help his son once he did reappear in the medical system. Even on a personal level, individual practitioners need guidance to sustain daily practice without burnout. Organizing gives rheumatologists and those involved in treating arthritis the collective expertise to advocate for their patients and increases public awareness about the diseases they treat. Educational resources on rheumatic diseases can be made available for allied health professionals, politicians, and the public. As a group, rheumatologists can lobby for necessary medication that is distributed in a safe manner. They can also explain that they have a special expertise that requires extensive education. They need to have a referral system in place so that patients with rheumatic conditions, such as rheumatoid arthritis or systemic lupus, can be seen in a timely fashion. In this way, they can promote a moral practice of medicine where principles of autonomy, beneficence, nonmaleficence, and justice are practiced. We end with a suggestion that rheumatologists organize in order to collectively devise ways to cope with the conditions unique to their own communities.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare they received no support from any additional organization for this work.

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Atlanto-axial instability in rheumatoid arthritis: a review

Omar ANA¹, Oyoo GO², Musau CK¹

Abstract

Objectives: The purpose of this literature review is to identify common lesions present in the rheumatoid neck with specific emphasis to atlanto-axial instability, review its clinical presentation, imaging findings and management.

Study design: A review of the English medical literature was done with focus on recent studies that covered the presentation, diagnosis, management and clinical outcomes of rheumatoid arthritis of the cervical spine specifically atlanto-axial instability.

Data extraction: A comprehensive literature review of the English medical literature was obtained through PubMed up to 2015 was performed identifying relevant and more recent articles that addressed the presentation, evaluation, surgical management and outcomes of rheumatoid patients with atlanto-axial instability.

Data synthesis: Atlanto-axial instability is a very debilitating disease with high morbidity and mortality if untreated. Onset of myelopathy is a poor prognostic factor with poor long-term survival. High index of suspicion and early intervention results in good outcomes and prevents neurological outcome.

Conclusion: Cervical spine involvement in rheumatoid arthritis is common and debilitating. Atlanto-axial instability is the commonest form. Early diagnosis and treatment is key in management. Early selective choice of patients for surgery results in better outcomes.

Introduction

Rheumatoid Arthritis (RA) is a chronic systemic inflammatory disease that primarily affects the joints. Although inflammatory arthritis of the small joints in the hands and feet is a common clinical manifestation, the cervical spine can also be affected. The first description of RA is found in the dissertation of Augustin Jacob Landré-Beauvais in 1800 in France when he first noticed the symptoms and signs of what we now know to be RA. He examined and treated a handful of patients with severe joint pain that could not be explained by other known maladies at the time (such as “rheumatism” or osteoarthritis)³⁴. Rheumatoid arthritis is the most common inflammatory disorder of the cervical spine. Cervical spine involvement is a highly characteristic component in RA and other chronic inflammatory rheumatic diseases³⁴.

In 1890, A. Garrod described 178 patients with cervical spine involvement in a series of 500 patients with RA⁵. The reported prevalence of cervical involvement in rheumatoid arthritis patients varies from 17-86%⁷⁸. The atlas-axis—cervical vertebrae 1 and 2 (C1 and C2)—articulation is one of the prime disease targets. The erosive pannus formation at this joint often leads to bony destruction and laxity in the surrounding ligamentous complex, especially the transverse ligament that aligns the atlas and axis. The subsequent loss of anchoring structures results in atlanto-axial subluxation (AAS)¹⁰. The subluxation can be anterior, posterior, lateral, and rotatory. The Anterior Atlanto-axial Subluxation (aAAS) is the most common subtype; the reported prevalence ranges from 10% to 55% followed by vertical subluxation and sub axial subluxation. The average female representation is 75%. The mean age at the time of outcome assessment was 58 years old (range of 33 to 69 years), and the mean disease duration was 12 years (range of 2 to 30 years)¹¹.

Clinical presentation

Clinical features are extremely variable. Sub-occipital pain is the commonest accounting for 40-85% of all patients and an early finding¹²-¹⁴. Pain that is worse when upright and relieved with recumbency is usually the result of compression of the greater occipital branch of C2, whereas
involvement of the auricular branch of C2 causes ear pain. Pain associated with subluxation is generally aggravated with neck motion, and patients may actually describe a clunking sensation or a feeling that their head is falling forward with flexion. Vague upper extremity clumsiness or weakness is also common, and patients have been described as often having difficulty finding the words to describe their symptoms. Vertebrobasilar insufficiency, especially with basilar invagination, may cause tinnitus, vertigo, and loss of equilibrium, visual disturbance and dysphagia.

L’Hermitte sign is provoked by flexing the head, and is associated with a palpable subluxation (“clunk test”). Marks and Sharp reported an average delay of 31 days between onset of neurological signs and diagnosis of myelopathy hence high index of suspicion is of great assistance. Early signs of myelopathy include clumsiness of the hands, gait disturbances and heaviness of the lower limbs. Patients who were initially ambulatory and become wheelchair bound should raise a suspicion of cervical spine involvement. Physical examination demonstrates weakness, spasticity and the presence of pathological reflexes. Less commonly patients present with features of vertebra-Basilar insufficiency which are variable.

**Imaging**

Aim of imaging is to help identify patients at risk of neurological injury and define cervical deformity and instability. Although progressive radiological deformities are seen in 43-86% of patients with rheumatoid arthritis, only 7-34% have neurological deficits. Plain radiograph forms the basis of initial evaluation of cervical involvement.

**Plain radiograph**

Screening X-rays include anterior-posterior, lateral, open mouth odontoid, dynamic flexion and extension lateral views. Overall bony alignment, degree of osteopenia and soft tissue shadows should be assessed. Particular attention should be paid to the anterior and posterior Atlanto-dental intervals (AADI and PADI, respectively), the amount of superior migration of the tip of the odontoid and degree of sub axial subluxation. Routine evaluation of the integrity of the atlanto-axial complex is best evaluated on the lateral flexion-extension radiographs. The classic measurements of AAS are seen on plain radiograph.

Anterior Atlanto-Dental Interval (AADI); is the distance from the posterior border of the anterior tubercle to the dens is less than 3mm in adults. It is measured on lateral radiograph. Greater than 8mm interval suggests rupture of the alar and transverse ligaments and is an indication for surgery.

Posterior Atlanto-Dental interval; evaluates the maximum amount of space available for the upper cervical spinal cord. It is a better predictor of spinal cord injury compared to AADI. It represents anterior-posterior diameter of the spinal canal at that level <14mm results in cord compression.

**Computed tomography**

Best modality for assessing bone anatomy is Multiplanar CT with 3D reconstruction. The reformatted sagittal CT scan can precisely document the position of the odontoid with respect to the foramen magnum, the degree of atlanto-axial dislocation, and the relationships among the upper cervical spine joints. CT also allows for accurate visualization of bony erosions, ankylosis, pseudarthrosis, and vertebral collapse, for planning best surgical technique and implant size. CT angiography is significant in evaluating vertebral artery anatomy.

**Magnetic resonance imaging**

Is the modality of choice for early cervical involvement and cord compression in RA because of excellent soft tissue details. It is important in assessing bony anatomy, the periodontoid pannus, brainstem, spinal cord and relationship of the odontoid to the foramen magnum. Pre/post contrast cervical MRI must be done in all patients. MRI can also be used to predict prognosis. T1-weighted spinal cord signal changes are associated with poor clinical status and also poor final postoperative outcome. MRI is also important in assessing cervicomedullary angle. A normal cervicomedullary angle is between 135-175 degrees and an angle below 135 degrees is associated with myelopathy.
<table>
<thead>
<tr>
<th>Modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain radiograph</td>
<td>Lower cost &amp; widely available&lt;br&gt;Screening of asymptomatic patients&lt;br&gt;Low radiation dose&lt;br&gt;Good for evaluation spinal alignment&lt;br&gt;Flexion &amp; extension allow visualization of occult instabilities</td>
<td>Poor anatomical detail, especially at craniocervical &amp; cervicothoracic junction&lt;br&gt;Poor soft tissue visualization&lt;br&gt;Poor visualization of bone erosions</td>
</tr>
<tr>
<td>CT Scan</td>
<td>Multiplanar widely available&lt;br&gt;Gold standard for bone evaluation&lt;br&gt;Good for evaluation of ankylosis &amp; pseudarthrosis&lt;br&gt;Useful for surgical planning&lt;br&gt;Flexion/extension for occult injuries</td>
<td>Higher cost compared to plain radiographs&lt;br&gt;Higher dose of radiation (relative contraindication during pregnancy)&lt;br&gt;Risks w/ intravenous injection of iodinated contrast&lt;br&gt;Requires sedation for young or claustrophobic patients&lt;br&gt;Poor evaluation of soft tissues &amp; spinal cord</td>
</tr>
<tr>
<td>MRI</td>
<td>Gold standard for soft tissue &amp; spinal cord evaluation&lt;br&gt;Most sensitive &amp; specific for cervical instabilities&lt;br&gt;Flexion &amp; extension allow visualization of occult instabilities&lt;br&gt;Best for evaluation of patients with neurological deficits</td>
<td>Highest cost of all imaging modalities&lt;br&gt;Requires sedation for young or claustrophobic patients&lt;br&gt;Risk w/ intravenous injection of gadolinium, especially in patients w/ kidney diseases (nephrogenic systemic fibrosis)&lt;br&gt;May be contraindicated in patients w/ implanted pacemakers, stimulators etc.</td>
</tr>
</tbody>
</table>

Management: non operative management

Patients education on the effects of rheumatoid arthritis on the cervical spine and myelopathy during the first encounter with spine surgeon. Disease Modifying Antirheumatic. Drugs (DMARDs) have been shown to reduce the progression of cervical disease hence important to emphasize role of drug compliance

Operative management

Indications for surgery: Clear surgical indications for patients with rheumatoid arthritis include persistent intractable pain and/or neurological deficits. Cervical collars do not prevent progression of cervical instability. Spinal cord compression is difficult to assess in patients with joint deformities and distal muscle weakness due to the disease hence progressive neurological compromise is an indication for surgery. Patients with radiological instability with minimal neurological deficit and pain provide a big challenge in management. Radiological evidence of cervical instability is common, but not all patients are at risk of neurological injury.

Surgical outcomes: Improved pre and post operative management, newer technologies with well chosen surgical patients has resulted in improved outcomes. Mizutani et al demonstrated that with appropriate selection, operative intervention can still provide good pain relief, preserve daily activities and improve the quality of life in the elderly patient with rheumatoid arthritis. Clinical success rate for cervical fusion ranges from 60-100% due to variability of the patient population, disease severity at surgical time and surgical technique familiarity. Onset of myelopathy results in increase in long term mortality and reduction in neurological recovery. The perioperative mortality for Ranawat 3B patients is 12.5% with the reported 1-year mortality rate after surgery approaching 61%.

Ranawat’s classification of neurological deficit:

<table>
<thead>
<tr>
<th>Class</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pain, no neurological deficit</td>
</tr>
<tr>
<td>2</td>
<td>Subjective weakness, hyperreflexia, dysesthesias</td>
</tr>
<tr>
<td>3</td>
<td>Objective weakness, long-tract signs present</td>
</tr>
<tr>
<td>3A</td>
<td>Ambulatory</td>
</tr>
<tr>
<td>3B</td>
<td>Non-Ambulatory</td>
</tr>
</tbody>
</table>

Conclusions

Atlanto-axial instability in rheumatoid patients is very common, highly progressive with devastating outcomes. Natural history of the disease results in increased morbidity and mortality. Myelopathy is a poor prognostic factor in above patients with poor survival outcome. Early diagnosis and treatment has been shown to correlate with good outcomes.
References


Echocardiographic findings in patients with rheumatoid arthritis attending the rheumatology clinic at the Kenyatta National Hospital

Ibrahim-Sayo EA, Oyoo GO, Ogola EN, Ilovi S

Abstract

Objectives: To determine the prevalence of echocardiographically detected cardiac abnormalities in patients with Rheumatoid Arthritis (RA) at Kenyatta National Hospital (KNH).

Design: Cross-sectional descriptive study.

Setting: Rheumatology clinic at Kenyatta National Hospital.

Subjects: One hundred and four rheumatoid arthritis patients who gave consent/assent.

Results: One hundred and four RA patients fulfilled the inclusion criteria with a mean age of 51 years and a female to male ratio of 25:1. The prevalence of echocardiographic abnormalities was found to be 62.5% and was unrelated to CDAI and duration of disease. The most common cardiac lesion was pericardial effusion at 39.4%. The tricuspid valve was the most commonly affected valve with 15.4% having Tricuspid Regurgitation (TR). Pulmonary hypertension was found in 5.5% of patients.

Conclusion: This study shows a high prevalence of cardiac abnormalities among RA patients despite these patients being on disease modifying medications and being diagnosed relatively earlier. Majority of the patients were in remission with duration of illness less than 5 years.

Introduction

Rheumatoid Arthritis (RA) is a progressive, systemic autoimmune disease characterized by chronic inflammation of multiple joints with associated systemic manifestations. RA is associated with many extra-articular clinical manifestations and various organ involvement including the skin, eye, heart, lung, hematopoietic tissue, renal, nervous and gastrointestinal systems. Extra-articular manifestations of RA occur in about 40% of patients, either at the beginning or during the course of their disease.

The disease is associated with a high risk for morbidity and premature death secondary to the earlier development of cardiovascular diseases. Cardiac manifestations are observed in RA patients and echocardiography is the method of choice to detect pathologies in the morphology and function of heart. A wide range of spectrum of cardiac abnormalities has been described in various cohorts of RA.

The most common cardiac involvement in RA is pericarditis and various studies have reported an increase in the prevalence in patients with seropositive RA and it is usually clinically silent. A study in South Africa done by Mody using two dimensional (2D) echocardiogram to determine the presence of pericardial effusion revealed a 6% prevalence in the RA cohort that was studied. Pericardial disease was detected in 5.5% of RA patients in a study done in Turkey using standard echocardiographic findings.

Myocardial disease in RA is typically clinically silent and only manifests as myocardial dysfunction after a prolonged preclinical phase. Manuela di Franco et al. studied 32 patients with RA in Italy and found left ventricular filling abnormalities characterised by a reduced transmitted flow velocity (E/A) ratio versus controls. They concluded that RA patients, in absence of clinical evidence of heart disease, show diastolic dysfunction characterised by impaired E/A and systolic/diastolic (S/D) ratio.

Cardiac tissues especially valve leaflets are extremely vulnerable to the process of inflammation and autoimmunity. In a study by Beckhauser et al., valve involvements in RA patients were investigated and 15.2% were recognized with valve disease. Valve damages were more common in patients whose disease was of more than 15 years duration and the aortic valve was most commonly involved. A study conducted by Guedes et al. revealed that the number of valves involved increased with advancing age but was unrelated to disease duration. Regurgitation is the most common form of valve disease,
although stenosis has been reported. The mitral valve was selectively involved in the RA patients studied by Guedes et al., and mitral valve disease was significantly more common in the RA group than in the control group.

Pulmonary involvement is common among patients with RA and has a variety of manifestations including pulmonary hypertension. Dawson et al. in the United Kingdom studied raised pulmonary artery pressures measured with doppler echocardiography in 146 RA patients. Twenty one percent of all the RA patients had pulmonary hypertension without significant cardiac disease or lung disease evident on pulmonary function testing.

Two dimensional (2D) echocardiography is a non-invasive procedure capable of displaying a cross-sectional view of the heart, including the chambers, valves and the major blood vessels that exit from the left and right ventricle. It is particularly useful in detecting various valvular lesions, measuring the left ventricular ejection fractions, determining myocardial wall abnormalities and also measuring the pulmonary pressures and detecting the presence of pericardial effusions.

Materials and Methods

The study population was RA patients on follow up at KNH. Current hospital records show that there are 146 RA patients attending the rheumatology clinic. A sample of RA patients derived from this finite population (n=104) was subjected to a non-invasive 2D echocardiograph for the determination of cardiac abnormalities. Consecutive sampling method was used to recruit patients with RA who visited the KNH Rheumatology Clinic.

Results

Between 16th December 2015 and 17th March 2016, 110 patients being managed for RA at KNH were screened for study eligibility, of these 104 subjects underwent a targeted history and examination and were booked for echocardiography either the same day or another day during the course of the week with 6 patients excluded. All 104 subjects had echocardiography studies done and were included in the analysis as depicted in Figure 1.

![Flow chart of patients screening and enrolment process](image)

A. Demographics and duration of disease: The mean age of the study sample was 51.0 years. The cohort in this study as expected was predominantly female with a ratio of 25:1. Majority of the patients had RA disease duration of > 1 year (84.6%) (Table1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.0 (16.4)</td>
</tr>
<tr>
<td>Duration of disease</td>
<td></td>
</tr>
<tr>
<td>Less than 1 year</td>
<td>16 (15.4)</td>
</tr>
<tr>
<td>1 to 5 years</td>
<td>48 (46.2)</td>
</tr>
<tr>
<td>6 to 10 years</td>
<td>31 (29.8)</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>9 (8.6)</td>
</tr>
</tbody>
</table>

B. Clinical variables: Fifty one percent of all patients were on at least 2 combination Disease Modifying Anti Rheumatic Drugs (DMARD’s) (45.2% on 2 and 5.8% on 3 DMARDs respectively). Forty nine percent of patients were on a single DMARD and the most frequently used DMARD was hydroxychloroquine. Frequency of patients on methotrexate was 22.2%. Leflunomide as the other DMARDs used by this population was 18.3% (Table 2).

<table>
<thead>
<tr>
<th>Number of drugs</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51 (49.0)</td>
</tr>
<tr>
<td>2</td>
<td>47 (45.2)</td>
</tr>
<tr>
<td>3</td>
<td>6 (5.8)</td>
</tr>
<tr>
<td>DMARDS</td>
<td></td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>39 (37.5)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>8 (7.7)</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>Hydroxychloroquine+ Methotrexate</td>
<td>9 (8.7)</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>38 (36.5)</td>
</tr>
</tbody>
</table>

C. Echocardiographic findings: The overall prevalence of cardiac abnormalities detected by echocardiography was 62.5% (CI 52.9 – 72.1) with the major contributors to this high prevalence being pericardial effusion and type 1 diastolic dysfunction. However both the pericardial effusion and type 1 dysfunction were regarded to as clinically insignificant because there were no associated features or echocardiographic feature of constrictive pericarditis or tamponade associated with the pericardial effusion and all the patients with type 1 diastolic failure were at NYHA grade 1 with no other features of decompenation (Table 3).
Table 3: Frequency of cardiac abnormalities

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>65(62.5)</td>
<td>52.9-72.1</td>
</tr>
<tr>
<td>Normal</td>
<td>39(37.5)</td>
<td>27.9-47.1</td>
</tr>
</tbody>
</table>

D. Pericardial assessment: Pericardial effusion was the most common abnormality detected among patients in the study with a prevalence of 39.4%. The pericardial effusion in this subset of patients was graded as mild effusion (<5mm) as it was not associated with clinical or echocardiographic feature suggestive of constrictive pericarditis. No pericardial thickening was observed in the study and none of the patients was found to have pericardial calcification on echocardiography.

Table 4: Pericardial abnormalities

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial effusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=104</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>41 (39.4)</td>
<td>34.0-53.2</td>
</tr>
<tr>
<td>Pericardial effusion size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5mm</td>
<td>102 (98.1)</td>
<td>95.2-100.0</td>
</tr>
<tr>
<td>&gt;10mm</td>
<td>2 (1.9)</td>
<td>0-4.8</td>
</tr>
</tbody>
</table>

E. Myocardial function: There was generally good systolic function among patients with only 2.9% of patients having systolic dysfunction characterized by an ejection fraction of less than 50%. Diastolic dysfunction on the other hand was more prevalent in this population of RA patients, with a prevalence of 22.1%, of which type I diastolic dysfunction was predominant (20.2%).

F. Valvular assessment: The overall prevalence of valvular abnormalities detected in the study population was 30.8%. The valvular abnormalities found in this cohort of RA patients were predominantly tricuspid valve regurgitation at 15.4%. All patients found to have tricuspid regurgitation had a mild regurgitation as it was not necessarily associated high pulmonary pressure. Mitral valve regurgitation was found in 5.8% and mitral stenosis in 1.9% of study patients. Among patients with mitral insufficiency, 66.7% had grade I mitral insufficiency and 33.3% had grade 2 insufficiency. 6.7% of patients were found to have aortic valve regurgitation and all were graded as mild regurgitation as it was not associated with LV dilatation (Table 5).

Table 5: Valvular abnormalities

<table>
<thead>
<tr>
<th>Variable</th>
<th>n =28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valvular abnormalities</td>
<td>28</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>6</td>
</tr>
<tr>
<td>Grade I</td>
<td>4</td>
</tr>
<tr>
<td>Grade II</td>
<td>2</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>2</td>
</tr>
<tr>
<td>Mild</td>
<td>2</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>7</td>
</tr>
<tr>
<td>Mild</td>
<td>7</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>0</td>
</tr>
<tr>
<td>Tricuspid regurgitation</td>
<td>12</td>
</tr>
<tr>
<td>Mild</td>
<td>9</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Stenosis</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary regurgitation</td>
<td>1</td>
</tr>
<tr>
<td>Mild</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>0</td>
</tr>
</tbody>
</table>

G. Pulmonary pressure: Of the 104 patients in the study, 5.5% had pulmonary hypertension of which only one patient was associated with pulmonary regurgitation.

H. Number of cardiac lesions: Fifty five point four percent of patients with cardiac abnormalities were found to have more than one abnormality (35.4% with 2 cardiac abnormalities and 13.0% with 3 cardiac abnormalities). Forty four point six percent of the patients had only one abnormality detected on echocardiograph.

Table 6: Number of cardiac abnormalities

<table>
<thead>
<tr>
<th>Number of cardiac abnormalities</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 65</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>29 (44.6)</td>
</tr>
<tr>
<td>2</td>
<td>23 (35.4)</td>
</tr>
<tr>
<td>3</td>
<td>13 (20.0)</td>
</tr>
</tbody>
</table>

I. Clinical Disease Activity Index (CDAI): Using the tool to determine the clinical activity 60.5% of all patients were in remission, 30.8% had low activity and only 8.7% had moderate activity.

J. Associations: The mean age at diagnosis was comparable between those who had cardiac abnormalities and those who do not have any cardiac abnormality at 51.5 and 50.2 respectively. This explorative study was not powered to make any associations between cardiac abnormalities, CDAI and duration of disease due to a small sample size. There was no association of overall cardiac abnormalities with the other variables in this study.
Patients with RA less than 1 year had cardiac abnormalities that are comparable to the general population (Table 7). The results of this study also did not show any association between cardiac abnormalities and the various drug combinations used in this cohort. Mild pericardial effusion being the most common abnormality detected in this cohort had no significant associations with both demographic and clinical variables.

Table 7: Associations of demographic and clinical variables with cardiac abnormalities

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cardiac abnormality</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, mean (SD)</td>
<td>Abnormal Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>51.5 (16.7)</td>
<td>50.2 (15.1)</td>
<td>0.701</td>
</tr>
<tr>
<td>CDAI</td>
<td>Remission Low activity Moderate activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>11 (68.8) 39 (61.9)</td>
<td>5 (31.2) 24 (38.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>1 to 5 years</td>
<td>29 (60.4) 19 (39.6)</td>
<td>19 (38.1) 13 (40.6)</td>
<td>0.7 (0.2-2.3) 1.0 (0.2-2.3)</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>18 (58.1) 7 (77.8)</td>
<td>2 (22.2) 2 (22.2)</td>
<td>0.6 (0.2-2.3) 1.6 (0.2-10.6)</td>
</tr>
</tbody>
</table>

Discussion

The overall prevalence of echocardiographic abnormalities amongst 104 RA patients was 62.5%. This represents a composite of pericardial, myocardial, valvular abnormalities and pulmonary hypertension. The whole spectrum of structural and functional cardiac abnormalities that could be evaluated by echocardiography was included in the study, as to provide data that could serve as the basis for future research on cardiac abnormalities in this cohort. The prevalence of cardiac abnormalities in our study is similar to a study done in South Africa by Schorn et al. who performed echocardiograph in 44 rheumatoid arthritis patients and showed a 73% overall cardiac abnormalities. A large number of patients in this study (55.4%) had more than one cardiac abnormality and this is also in keeping with the natural history of the chronic inflammatory state of the disease affecting all structures of the heart and the combination DMARD’s used amongst these patients.

The high prevalence was mostly driven by clinically insignificant pericardial effusion and type 1 diastolic dysfunction. The pericardial effusion was graded as mild effusion as the size was less than 5mm. Type 1 diastolic dysfunction is a nonspecific echocardiographic finding. 20.2% of the study population with no associated clinical features suggestive of overt heart failure. Schorn et al. found pericardial effusion in 32% in RA patients studying a similar spectrum of structural and functional cardiac abnormalities. Macdonald et al. in California performed echocardiographic studies on 51 RA patients in a cross sectional study and reported 31% mild pericardial effusion. Pericardial disease was detected in 5.5% of RA patients in a study done in Turkey using standard echocardiographic findings. Our study reports a high prevalence of subclinical pericardial effusion at 39.4% which could be explained by both the natural history of the disease and the various combinations of disease modifying agents used for these patients (Hydroxychloroquine, Methotrexate, etc). No pericardial thickening or calcification was noted in any of the patients.

Myocardial dysfunction in RA is a consequence of several factors including direct inflammatory process of RA on the myocardium, premature atherosclerosis and side effects of some of the medications used to treat the condition, specifically cardiotoxicity related to hydroxychloroquine use. Literature suggests that myocardial dysfunction in RA patients presents predominantly as diastolic dysfunction and in the majority of patients it is asymptomatic. In our study a generally good LV function among RA patients is reported with only 2.9% having mild LV dysfunction. 20.2% of RA patients at KNH had a type 1 diastolic dysfunction and this is much lower compared to a study done by Gabriel et al. in USA who did a cross sectional community based study comparing adults with and without RA and without clinical evidence of heart failure using 2D echocardiography. Their study included 244 subjects with RA with a mean age of 60.5 years wherein they reported a 31% diastolic dysfunction which had a positive association with duration of disease. Diastolic dysfunction in our study was not found to be associated with a prolonged duration of RA even though the natural course of diastolic function is known to deteriorate with time. Furthermore, there are no associations found between diastolic dysfunction and use of disease modifying drugs. In this study confounders such as hypertension was not assessed for but the relatively high prevalence of diastolic dysfunction should be a cause for concern because of the potential to progress to overt diastolic heart failure. Diastolic heart failure preferably denoted as heart failure with preserved ejection fraction is frequently encountered in the older patients with multiple comorbidities and associated with similar mortality rates as heart failure with reduced ejection fraction.

In a study by Beckhauser et al., valve involvements in RA patients were investigated and 15.2% were recognized with valve disease. Valve damages were more common in patients whose disease was of more than 15 years duration and the aortic valve was most commonly involved. Valvular involvement reflects the chronic inflammatory state of the disease. There was no relationship between valve involvement and gender, age, exposure to tobacco, positive RF, presence of ANA, rheumatoid nodules, and anti-cardiolipin antibodies. Our study found a high prevalence of valvular involvement compared to other studies at 30.8%. The valvular abnormalities found in this cohort of RA patients were predominantly tricuspid valve regurgitation at 15%. Tricuspid regurgitation in this cohort was mild as determined by the echo criteria it was not
associated with pulmonary hypertension hence it may be considered to be due to the effect of RA on the valves. From our study we cannot determine the exact reason for this high prevalence of tricuspid valvular regurgitation in this population. We did not find any association between valvular abnormality and disease duration, age at diagnosis or clinical features; however our study was not powered to assess for these associations.

Dawson et al\textsuperscript{12} in the United Kingdom studied raised pulmonary artery pressures measured with doppler echocardiography in 146 RA patients and 21\% of all the RA patients had pulmonary hypertension without significant cardiac disease or lung disease evident on pulmonary function testing. We report a much lower prevalence of pulmonary hypertension at 5.5\% with no significant association between raised pulmonary pressure and any of the demographic or clinical variables evaluated. This was graded as mild pulmonary hypertension as it was not associated with echocardiographic and clinical evidence of an associated right ventricular enlargement or right valvular lesions. Our study population was recruited at an outpatient basis and may therefore have been skewed toward the less severe end of the disease spectrum as compared with the overall population of RA patients thus explaining the above mild and clinically insignificant findings.

References

Certolizumab effect in a cohort of 60 Libyan patients with rheumatic diseases

Elhabbash B, Tarsin R

Abstract

Background: Tumour Necrosis Factor (TNF) has a central role in the pathogenesis of Rheumatoid Arthritis (RA), mediating both inflammation and joint damage. Certolizumab Pegol (CZP) is a PEGylated Fab fragment of a humanized anti-TNF antibody with high affinity to TNF.

Objective: The study was done to monitor the effects and side effects of certolizumab on our Libyan patients with rheumatic diseases.

Methods: The inclusion criteria for the study were all patients with rheumatic diseases who were treated by certolizumab in the period from August 2014 to August 2016 in Rheumatology Department, Tripoli Medical Center, Tripoli, Libya. They were 60 patients, 43 of them had RA, 14 patients had Ankylosing Spondylitis (AS), 2 patients had Psoriatic Arthropathy (PsA) and 1 patient had enteropathic arthritis. Certolizumab 400mg subcutaneous was given at week 0, 2, 4 and then 400mg every 4 weeks. Demographic details such as age and sex were recorded. Clinical characteristics as rheumatoid factor in RA patients, disease duration, duration of taking certolizumab and drugs used before starting certolizumab were noted. Assessment of disease activity was measured by DAS28 for RA patients, by BASDAI for AS patients and by DAPsA for PsA patients. For all patients, complete blood count, erythrocyte sedimentation rate, liver function test, hepatitis screen, urine routine examination and tuberculin test before starting certolizumab were requested to monitor its side effects during follow up.

Results: Forty three patients had rheumatoid arthritis, their mean age was 44.6±SD10.67 years, 11.6% were male and 88.3% were female. Rheumatoid factor was positive in 58%, negative in 19% and unknown in 23%. Fourteen patients were ankylosing spondylitis; their mean age was 34.9±SD8.22 years, 85.7% were male and 14.2% were female. Two patients had psoriatic arthritis, mean age was 43.5±SD16.26 years, one was female and the other was male. One patient had enteropathic arthritis; she was a female aged 57 years. All RA patients were on prednisolone and/or one or two DMARD before starting CZP and failed to show response. All AS patients were on one or two NSAIDs and/or salazopyrine and failed to show response before starting CZP. One psoriatic arthritis patient was on leflunomide and methotrexate (MTX) and the other was on MTX alone. Enteropathic arthritis patient was on MTX, azathioprine and salazopyrine. The mean of DAS28 before starting CZP for RA patients was 4.9±SD1.15 and the mean of DAS28 at the last dose was 3.1±SD1.12 (P value<0.0001). The mean of BASDAI before using CZP was 4.2±SD1.61 and the mean of BASDAI at the last dose was 1.7±SD1.86 (P value <0.0012). Both PsA patients had moderate disease activity (mean of DAPsA=20±SD1.6) and became (mean of DAPsA=6±SD1.2) which means low disease activity (P value <0.0002). Enteropathic arthritis patients showed significant improvement regarding gastrointestinal symptoms and arthritis. Regarding side effects of certolizumab pegol, one female RA patient developed tuberculosis lymphadenitis and one male RA patient had hypersensitivity reaction.

Conclusion: During two years of follow up of our rheumatic diseased patients on certolizumab, we noticed a significant improvement in disease activity scores with minimal side effects.

Introduction

Tumour Necrosis Factor (TNF) has a central role in the pathogenesis of Rheumatoid Arthritis (RA), mediating both inflammation and joint damage. TNF inhibitors revolutionised the management of RA because these agents improve signs and symptoms and physical function and inhibit structural damage, particularly in combination with methotrexate (MTX).
Certolizumab Pegol (CZP) is a PEGylated Fab fragment of a humanized anti-TNF antibody with high affinity to TNF. It lacks an Fc region and may thus avoid potential Fc-mediated effects such as complement- or antibody-dependent, cell-mediated cytotoxicity, which have been seen in vitro, and attachment of the PEG moiety to the Fab fragment yield a molecule with a plasma half-life of about 2 weeks.

Certolizumab pegol gained FDA approval in September/October 2013 for two new indications, adult with active Psoriatic Arthritis (PsA) and adult with active Ankylosing Spondylitis (AS). It was already approved for adults with Crohn’s disease and rheumatoid arthritis.

Under current ASAS/The European League Against Rheumatism (EULAR) recommendations, Non-Steroidal Anti-Inflammatory Drugs (NSAID) are the first-line treatment option for axial spondyloarthritis patients. In patients with inadequate response to ≥2 NSAIDs for ≥4 weeks in total, TNF inhibitor therapy is recommended for AS patients.

Materials and Methods

The inclusion criteria for the study were all patients with rheumatic diseases who were treated by certolizumab in the period from August 2014 to August 2016 in Rheumatology Department, Tripoli Medical Center, Tripoli, Libya. They were 60 patients, 43 of them had RA, 14 patients had AS, 2 patients had PsA and 1 patient had enteropathic arthritis.

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

Certolizumab 400mg subcutaneous was given at week 0, 2, 4 and then 400mg every 4 weeks. Demographic details such as age and sex were recorded. Clinical characteristics as rheumatoid factor in RA patients, disease duration, duration of taking certolizumab and drugs used before starting certolizumab were noted. Assessment of disease activity was measured by DAS28 for RA patients, by BASDAI for AS patients and by DAPSA for PsA patients. Disease activity scores were measured at the start of certolizumab and every injection thereafter.

For all patients, complete blood count, erythrocyte sedimentation rate, liver function test, hepatitis screen, urine routine examination and tuberculin test before starting certolizumab were requested to monitor its side effects during follow up.

Data was analysed using SPSS computer software package. The mean and standard deviations of the age, disease duration and duration of taking certolizumab were calculated. P value to measure if there is significant difference between the means of DAS28, BASDAI or DAPSA (according to the patient either RA, AS or PsA) at the start of certolizumab and at the last follow up were calculated using t-test.

Results

All patients with rheumatic diseases who took CZP in the period between August 2014 and August 2016 were included in the study. Forty three patients had rheumatoid arthritis, their mean age was 44.6±SD10.67 years, 11.6% were male and 88.3% were female. Rheumatoid factor was positive in 58%, negative in 19% and unknown in 23%. Fourteen patients had ankylosing spondylitis; their mean age was 34.9±SD8.22 years, 85.7% were male and 14.2% were female. Two patients had psoriatic arthritis, mean age was 43.5±SD16.26 years, one was female and the other was male. One patient had enteropathic arthritis; she was a female aged 57 years.

The mean duration of rheumatic diseases and the mean duration of taking CZP are shown in Table 1. All RA patients were on prednisolone and/or one or two DMARD before starting CZP and failed to show response. All AS patients were on one or two NSAIDs and/or salazopyrine and failed to show response before starting CZP.

Table 1: Mean duration of rheumatic diseases and the mean duration of taking Certolizumab pegol (CZP)

<table>
<thead>
<tr>
<th>No. of patients (n=60)</th>
<th>Mean of disease duration</th>
<th>Mean duration of taking CZP</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA (43 patients)</td>
<td>7.3±SD3.34 years</td>
<td>10.46±SD 2.60 months</td>
</tr>
<tr>
<td>AS (14 patients)</td>
<td>7±SD2.7 years</td>
<td>16.07±SD 3.08 months</td>
</tr>
<tr>
<td>PsA (2 patients)</td>
<td>2±SD1.18 years</td>
<td>7.5±SD1.45 months</td>
</tr>
<tr>
<td>Enteropathic arthritis (1 patient)</td>
<td>Duration=2 years</td>
<td>Duration=6 months</td>
</tr>
</tbody>
</table>

One psoriatic arthritis patient was on leflunomide and methotrexate (MTX) and the other was on MTX alone. Enteropathic arthritis patient was on MTX, azathioprine and salazopyrine. Table 2 shows different rheumatic diseases and different drug regimens used for them. The mean of DAS28 before starting CZP for RA patients was 4.9±SD1.15 and the mean of DAS28 at the last dose was 3.1±SD1.12.
Table 2: Shows different rheumatic diseases and different drug regimens used for them

<table>
<thead>
<tr>
<th>Drug regimen</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis patients</td>
<td>Total n=43 patients</td>
</tr>
<tr>
<td>Methotrexate MTX alone</td>
<td>16</td>
</tr>
<tr>
<td>MTX+ Hydroxychloroquine HCQ</td>
<td>8</td>
</tr>
<tr>
<td>MTX+ Salazopyrine SZP</td>
<td>3</td>
</tr>
<tr>
<td>HCQ alone</td>
<td>4</td>
</tr>
<tr>
<td>Prednisolone alone</td>
<td>1</td>
</tr>
<tr>
<td>SZP alone</td>
<td>1</td>
</tr>
<tr>
<td>Leflunomide alone</td>
<td>6</td>
</tr>
<tr>
<td>Leflunomide+ SZP</td>
<td>2</td>
</tr>
<tr>
<td>MTX+ leflunomide</td>
<td>2</td>
</tr>
<tr>
<td>Ankylosing spondylitis patients</td>
<td>Total n=14 patients</td>
</tr>
<tr>
<td>NSAID</td>
<td>12</td>
</tr>
<tr>
<td>Salazopyrine</td>
<td>2</td>
</tr>
<tr>
<td>Psoriatic arthritis patients</td>
<td>Total n=2 patients</td>
</tr>
<tr>
<td>Leflunomide+ MTX</td>
<td>1</td>
</tr>
<tr>
<td>MTX alone</td>
<td>1</td>
</tr>
<tr>
<td>Enteropathic arthritis patient</td>
<td>One patient</td>
</tr>
<tr>
<td>Azathioprine+ Salazopyrine + MTX</td>
<td>1</td>
</tr>
</tbody>
</table>

P-value showed extremely statistically significant difference between the two means which was (P value<0.0001). The mean of BASDAI before using CZP was 4.2±SD1.61 and the mean of BASDAI at the last dose was 1.7±SD1.86. These results showed a very statistically significant difference between the two means P value<0.0012. Both PsA patients had moderate disease activity (mean of DAPsA=20±SD1.6) and became (mean of DAPsA=6±SD1.2) which means low disease activity (P value <0.0002) (Table 3).

Table 3: Activity scores of different rheumatic diseases at start and at the last dose of certolizumab

<table>
<thead>
<tr>
<th>Type of rheumatic disease</th>
<th>At start of certolizumab</th>
<th>At last dose</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>4.9± SD1.15</td>
<td>3.1± SD1.12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean of DAS28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td>4.2±SD1.61</td>
<td>1.7±SD1.86</td>
<td>&lt;0.0012</td>
</tr>
<tr>
<td>Mean of BASDAI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PsA</td>
<td>20± SD2.6</td>
<td>6±SD1.2</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>Mean of DAPsA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Enteropathic arthritis patients showed significant improvement regarding gastrointestinal symptoms and arthritis. Regarding side effects of certolizumab pegol, one female RA patient developed tuberculous lymphadenitis at the fifth dose of CZP and one male RA patient had hypersensitivity reaction after the first dose.

Discussion

Certolizumab pegol is a PEGylated humanized Fab monoclonal antibody that targets and neutralizes both membrane bound and soluble tumour necrosis factor preventing inflammation and consequently the destruction of cartilage and bone19. Interestingly the Fc portion, which is lacking in CZP, is not necessary for TNF inhibitor to be clinically effective in RA. Thus, the primary mode of action of TNF inhibitor in RA does not appear to involve Fe-mediated effect but rather the binding and inactivation of TNF and probably reverse signalling which can also be mediated by Fc–free Fab molecule20,21.

Certolizumab pegol has a relatively long elimination half-life of two weeks, allowing subcutaneous administration once every two or four weeks19. Certolizumab pegol provided rapid, significant and clinically meaningful improvement in physical function and quality of life, with significant changes in HAQ-DI at week 1 and week 12, which continued to improve through to week 2422.

As functional outcomes are associated with structural damage in progressive RA, treatments as CZP that can both improve physical function and inhibit joint damage may help prevent long-term disability23-25.

Treatment with certolizumab pegol plus methotrexate were associated with significant greater improvement in DAS28 from baseline versus placebo at all time points (p<0.001)22. In our patients with RA a significant improvement in DAS28 at the start of treatment and the last dose was observed (p<0.0001).

Landewe et al26, observed that at week 12, statistically significant higher proportion of patients in certolizumab 200mg every 2 weeks (57.7%) and certolizumab 400mg every 4 weeks group (63.6%) achieved an ASAS20 response compared with placebo (38.3%) (P= 0.004 and p< 0.001) respectively. Landewe et al26 also noted that certolizumab treatment resulted in significant improvement in BASFI, BASDAI and BASMI linear versus placebo ((p<0.001) and improvement in BASFI, BASDAI and BASMI linear were similar between certolizumab treatment arms and observed from week 126.

In our study the mean of BASDAI of our patients at the start of certolizumab was 4.2± SD 1.6 and BASDAI at last close was 1.7 ± SD 1.86, this difference between the two means was very statistically significant P<0.0012. Certolizumab pegol had an acceptable safety profile with a low incidence of discontinuation due to adverse events22. Serious infections, including tuberculosis were reported more frequently with certolizumab pegol than placebo, consistent with rates associated with other anti- TNF treatment27. In our study tuberculosis was recorded in one patient (1.6%) and hypersensitivity reaction occurred in one patient (1.6%) indicating high safety profile of certolizumab.

Conclusion

During two years of follow up of our rheumatic diseased patients on certolizumab, we noticed a significant improvement in disease activity scores with minimal side effects.
Acknowledgement

To Amna Elhabbash, statistical analyzer, Faculty of Science, Tripoli University.

References


Sjogren’s Syndrome (SS) is a systemic autoimmune disorder, characterized by lymphocytic infiltration and malfunction of the exocrine glands. When it presents alone, it is referred to as primary Sjogren’s syndrome and secondary when presented in the context of an underlying connective tissue disease. The main clinical symptoms are dry eyes and xerostomia. A number of auto-antigens and auto-antibodies have been described which may play a central role in the pathogenesis of the disease.

Methodology: This was a retrospective study of all the rheumatology cases over a three year (January 2011-December 2013) period. The records of cases suggestive of Sjogren’s syndrome were retrieved for further study. Necessary information was derived from cases that met the diagnosis of Sjogren’s syndrome. Diagnosis was made based on symptomatology of dry eyes and dry mouth and the Ophthalmologist’s assessment in patients with an established diagnosis of connective tissue disorder.

Results: Six patients met the diagnosis of Sjogren’s syndrome out of the 472 rheumatology cases seen, constituting 1.27% of the total cases of rheumatology seen over the study period. There were 5 females (83.3%) and a male (16.7%). Twenty one were cases of rheumatoid arthritis of which six developed dry mouth and eyes suggestive of Sjogren’s syndrome.

Conclusion: Sjogren’s syndrome is not a common disorder in our clinic; it is preponderant in females and related to rheumatoid arthritis, it should also be considered in patients with other types of connective tissue disorders when they present with eye and mouth symptoms.

Introduction

Sjogren’s Syndrome (SS) is a multi-systemic disorder characterized by the destruction of lacrimal and salivary glands—glandular tissues resulting into keratoconjunctivitis Sicca (KCS), (dry eyes) and Xerostomia (dry mouth) respectively (Sicca syndrome)¹. Primary SS presents in isolation with KCS and Xerostomia. Secondary SS is commonly associated with Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), and Systemic Sclerosis (SSc)²,³.

SS affects all age groups with onset usually in the middle age. In Western studies, it has a prevalence of 4 per 100,000 populations and affects mostly females with a male to female ratio of 1:9⁴. The prevalence in African population is unknown.

The aetiology and pathophysiology are unknown. In primary SS, antibodies to ribonucleoproteins Ro (SS-A) and La (SS-B) are found in 90% of patients⁵. Viral infections have been implicated in its aetiology, including Epstein-Barr virus, hepatitis C virus, and cytomegalovirus⁶. Diffuse Idiopathic Infiltrative Lymphocytic Syndrome (DILS) is an important Sjogren mimic associated with Human immunodeficiency virus-1.

Clinical features of SS include decreased tear and saliva secretion, leading to dry eye and dry mouth. Salivary and extra-salivary B cell lymphomas have been found to be associated with SS. Systemic involvement may include the skin, respiratory, renal, hepatic, neurologic, and vascular system⁶.

The purpose of this study was to establish the prevalence of the Sicca syndrome in Nigerian patients with rheumatic disease.

Materials and Methods

We retrospectively reviewed the records of all 472 patients with rheumatic disorders seen at the medical outpatient clinic of Olabisi Onabanjo University Teaching Hospital (OOUTH) from January 2011 to December 2013. All RA patients were evaluated for evidence of SS according to the 2002 revised international classification criteria. For all patients, the diagnosis of RA was ascertained using established classification criteria⁷ and the disease onset and duration noted.

The following features were retrieved from the case records: arthritis, fever, rash, lymphadenopathy, parotid gland enlargement, xerostomia, xerophthalmia,
pulmonary symptoms, renal symptoms, nervous system involvement, hypertension and diabetes mellitus.

**Laboratory and radiological findings:** All patients had serological evaluations, including Antinuclear Antibody (ANA), anti-SSA and anti-SSB antibodies, Rheumatoid Factor (RF) in addition to full blood count (definition of terms are: anaemia (Hb<10 g/dl), leucopenia (white blood cell count <4000/µl), thrombocytopenia (platelet count <100,000/µl), electrolyte, urea and creatinine, chest-X-ray, and blood sugar estimation. Erythrocyte sedimentation rate was also checked. There was however no materials to detect the objective reduction in salivary secretion.

**Case definition:** The American-European consensus group criteria of 2002 for SS consist of six items which are:
- Ocular symptoms of inadequate tear production
- Ocular signs of corneal damage due to inadequate tearing
- Oral symptoms of decreased saliva production
- Salivary gland histopathology demonstrating foci of lymphocytes
- Tests indicating impaired salivary gland function
- Presence of auto-antibodies (anti-Ro/SSA and/or anti-La/SSB)

Primary SS was defined as patients with no associated connective tissue disease who have four of the above items (presence of auto-antibody is mandatory). Secondary SS was defined as the presence of any connective tissue disease in the presence of any four of the above items.

**Rheumatoid Arthritis (RA):** RA was defined according to the 1987 classification criteria of the American College of Rheumatology.

**Results**

Six patients fulfilled the criteria for SS among the 21 RA patients identified (4.4% of total rheumatology cases). All had developed SS following the onset of RA.

There were five females (83.3%) and one male. The age range of the patients was 35 to 53 years. All the patients presented with dry eyes and dry mouth. Other clinical features presented by our patients are as shown in Figure 1. Tear Break Up Time (TBUT) was 5 and 6 seconds respectively in 2 patients, 9 seconds in 3 patients and 10 seconds in one patient.

**Laboratory:** All patients had an elevated ESR, two had a significantly raised ANA titre and one a positive RoSSA/LaSSB. All the six patients had leucopenia, thrombocytopenia, and anaemia. Interstitial lung disease was seen in a female, two showed laboratory results in support of renal involvement (elevated creatinine and urea levels and two positive proteinuria) but none develop renal failure. None of the patients had diabetes mellitus.

**Medications:** Response to artificial tear (tear natural, Ivymoicell), artificial saliva, and muscarinic agent was uniformly good except for two patients who reacted to pilocarpine with diarrhoea and tremor respectively. The diarrhoea got better with continuation of the drug while tremor responded to dosage reduction.

**Figure 1:** Other clinical presentations of SS in our patients

<table>
<thead>
<tr>
<th>Ocular</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritation of the eye</td>
<td>Difficulty in swallowing solid foods</td>
</tr>
<tr>
<td>Grittiness/ sandy feeling in the eyes</td>
<td>Dental carries</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>Inability to speak for a long time without sipping water</td>
</tr>
<tr>
<td>Itchy eyes</td>
<td>Abnormal tear break up time</td>
</tr>
</tbody>
</table>

**Discussion**

Sjogren’s Syndrome (SS) often coexists with other systemic autoimmune diseases, including RA and systemic lupus erythematosus. In 1933, Sjogren described clinical and histological findings in nineteen women with dry mouth and dry eyes, thirteen of the patients had probable RA. Since 1965, there have been several studies that have focused on RA associated with SS. Subsequent studies demonstrated significant differences in the clinical features of SS patients with and without RA. In our study 28.6% of the 21 rheumatoid arthritis patients fulfilled the SS criteria, a value in agreement with earlier studies in other populations.

All the six RA/SS patients in this study presented with ocular manifestations. Early diagnosis of ophthalmic disease in patients with RA is very important because of the need for timely management of potentially serious and sight-threatening complications. The presence of ocular disease may also be an indication of on-going systemic disease activity.

The clinical course of ocular disease in RA is quite variable. Keratoconjunctivitis Sicca (KCS) due to SS is the most common ophthalmic manifestation of RA, occurring in as many as 15-25% of patients. Symptomatic and objective signs of KCS are central to the diagnosis of SS. Patients with SS often complain of dryness, foreign body sensation, burning, or photophobia and ocular examination usually reveal an abnormal tear break up time. Severe dry eye may however exist independently from severe articular disease and should be evaluated in all patients with RA regardless of extra-articular manifestations.

Sicca symptoms are much more common than SS in older adults. It was estimated that approximately 35% of older subjects have the sensation of dry eyes and dry mouth. This has been adduced to various medications.
prescribed for the elderly patients; however, only about 10% of these subjects have objective evidence of reduced tear or saliva production\textsuperscript{16}. Evidence of severe dry eye existed in 33% of the patients in this study. This finding is at variance with the finding in elderly patients, because the cohorts in this study were patients that are much younger and had secondary SS.

Other ocular manifestations seen in RA patients apart from KCS include episcleritis, scleritis, corneal inflammation and corneal infection\textsuperscript{6}. These clinical findings were however not established in our patients.

The diagnosis of dry/sicca symptom was confirmed by the Ophthalmologists in our patients with slit lamp evidence of abnormal tear break up time. Other ocular tests to confirm the sicca symptoms include Schirmer’s and Rose Bengal tests\textsuperscript{17} which were not done in our centre.

All the patients also presented with oral dryness (xerostomia) with difficulty in swallowing dry food without drinking liquids. Two patients had tooth extraction as a result of dental carries. Dry mouth is common particularly in older patients, but objective evidence of reduced salivary flow is less frequent\textsuperscript{18}. Salivary gland biopsy is not necessary in all patients for the confirmation that symptoms of dryness are due to SS\textsuperscript{21}. The presence of a connective tissue disease with diagnosis of KCS is enough to establish the diagnosis of secondary SS in patients with dry mouth symptoms\textsuperscript{19}.

All the six secondary SS patients had haematological abnormalities. They all presented with pan-cytopenia. Primary SS patients and RA without Sjögren’s, and RA with SS patients can present with a variety of haematologic abnormalities, including anaemia, leucopenia and thrombocytopenia\textsuperscript{20}. Earlier studies found that RA/SS patients had a longer duration of disease than those with RA only.

Patients with RA/SS have a more severe form of arthritis, and that the incidence of anaemia was higher in RA/SS patients than in RA patients\textsuperscript{21}. Leucopenia and thrombocytopenia in RA without SS is often associated with drug toxicity. Leucopenia and thrombocytopenia are frequently seen in RA/SS and primary SS, but seldom in RA only. Generally, the incidence of haematological system abnormality is much higher in RA/SS patients than in those without RA\textsuperscript{21}.

The six patients were treated with Disease Modifying Anti-Rheumatic Drugs (DMARD), and in addition were also placed on treatment for the Sicca symptoms. There is however no consistently effective treatment for SS. The current therapy is primarily symptomatic\textsuperscript{22}. Non-pharmacological modalities of treatment instituted for the ocular symptoms in our patients included avoidance of medications that can cause dryness and reduced exposure to environments that exacerbate dryness. Pharmacological therapies instituted include the use of artificial tear, occasional use of topical steroid during intense inflammation, and the use of pilocarpine. The symptoms of dry mouth were treated with frequent sips of water, intense oral hygiene, prevention and treatment of oral infections, and local and systematic stimulation of salivary secretion by the use of muscarinic agonist (pilocarpine).

People with xerostomia often have a very high rate of tooth decay and mucosal infection. Referral to the dentist should be early for recognition and treatment of dental carries. Proper brushing, flossing and use of alcohol-free mouthwashes should be recommended\textsuperscript{23,24}.

The good response observed in our patients with the use of muscarinic agonist may also in part be explained by the fact that all the patients were placed on hydroxy-chloroquine for the treatment of RA. Hydroxy-chloroquine has been shown to some extent to be beneficial for dry mouth\textsuperscript{21}. None of the patients however developed hydroxy-chloroquine induced maculopathy. A study of forty patients who received hydroxy-chloroquine (6-7mg/kg/day) for 24-48 months were shown to develop improvement in oral dryness compared with baseline values\textsuperscript{25}.

In conclusion, SS may be primary or secondary. RA is the most common underlying condition in secondary disease. Treatment should be a collaborative effort involving the ophthalmologists, dentists, and the rheumatologists.

References


Knowledge of health care workers on corticosteroid adverse drug events in rheumatologic, respiratory and dermatologic clinics in a teaching hospital in Nairobi, Kenya

Illovi CS¹, Mecha JO¹, Kigamwa P², Mutai K³, Mwachinga M¹, Genga EK¹, Sheikh A¹, Owino B¹, Wanjau W¹, Munyao T¹, Oyoo GO¹

Abstract

Background: Corticosteroids form the cornerstone of management for a myriad of rheumatological, dermatological and chronic respiratory tract diseases. Whereas these drugs are crucial in reducing morbidity and mortality, they are not without inherent grave risks. Health Care Workers (HCWs) providing care to patients on long term corticosteroids are required to be well versed with these Adverse Drug Events (ADEs). Kenyatta National Hospital, the teaching hospital of the University of Nairobi, has established rheumatology, respiratory and dermatology clinics. Corticosteroid prescribing and dispensing is provided by the doctors and pharmacy staff respectively with ADEs surveillance and patient education provided by these two cadres as well as the nurses as per standards of practice. As biologic agents are not yet available in these clinics, corticosteroids, as well as other immunosuppressant drugs remain vital in control of immunological diseases.

Materials and Methods: HCWs in these clinics were requested to complete a self-administered questionnaire assessing their knowledge of corticosteroid ADEs. The questions were open ended and the answers given were first analysed into total number of correct answers. Further analysis was done by grouping the correct answers into categories as per the systems affected by corticosteroids. A cut-off point of 6 correct answers was deemed adequate knowledge of ADRs. Correct answers given were calculated as a proportion of all the answers provided by the respondent. Median (interquartile range- IQR) was used to provide the midpoint of correct responses and the spread of the second and third quartiles respectively.

Results: Sixty-two HCWs were recruited, comprising of nurses (21%), pharmacy staff (12.9%) and senior house officers (66.1%). Majority (79%) had been stationed for over 1 year in the study clinics with 45% of them having worked in more than one of the study clinics. ADRs of corticosteroids: Median (IQR) number of correct responses was 6.0 (3.0-9.5). Only 61% identified ≥5 ADRs. Proportion of respondents who documented the various ADRs; Metabolic disorders 89%, cutaneous 61%, mineral bone disease 37%, GIT 36%, neuropsychiatric 32%, adrenal suppression 24%, ophthalmic 21%, myopathy 18%.

Drugs that potentiate the ADRs of corticosteroids: Median (IQR) number of correct responses was 1.0 (1.0-2.0). Proportion of respondents who identified the drugs; Cytotoxics 34%, NSAIDs 35%, anticoagulants 15%, others 10%.

Advice that should be given to patients on corticosteroids: Median (IQR) number of correct responses was 2.0 (2.0-3.0). Surveillance for ADRs- 53% , adherence to duration and dosage 48%, tapering of corticosteroids 32%, drug interactions 16%, drugs to counter corticosteroid ADRs 13%, steroid cards 7%.

Conclusion: Although HCWs routinely administer corticosteroids, the awareness of ADRs and potential drug interactions is low. This needs to be addressed in order to ensure adequate surveillance of ADRs.

Introduction

Immunological and inflammatory diseases, the bulk of which fall under the realm of rheumatology, pulmonology and dermatology, cause a great deal of morbidity and mortality. For decades, corticosteroids have formed the cornerstone in management of these diseases, even in the era of novel immunosuppressants and biological agents. This may be attributed to the fact that corticosteroids are highly effective in addition to being widely available and accessible. This is more so in low to middle income countries where the prohibitive cost of biological immunosuppressant agents limit their adoption.
Corticosteroids have two main effects; mineralocorticoid and glucocorticoid effects. Mineralocorticoid effects, via aldosterone production, regulate salt and water metabolism. Glucocorticoid effects are exerted through glucocorticoid receptor which is widely expressed in the human body, particularly on immune cells. They modulate the immune, cardiovascular, endocrine and metabolic systems.

Synthetic corticosteroids are analogues of endogenous steroids produced by the adrenal gland. Synthetic corticosteroids can be administered in near physiological doses to treat adrenal insufficiency, or in higher (pharmacologic) doses to treat underlying immune disorders. Different synthetic steroids have varying effects; with prednisone, dexamethasone and methylprednisolone having predominantly GC effects while fludrocortisone has mostly mineralocorticoid effects. Cortisone and hydrocortisone have been found to have both GC and MC effects and are therefore preferred in cases of adrenal insufficiency whereas those with GC effects are mostly used for their anti-inflammatory effects.

Common conditions treated with pharmacologic synthetic corticosteroids in our setup include Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), vasculitis; moderate to severe asthma, chronic obstructive pulmonary disease, interstitial lung disease; and dermatitis. Although each route of administration has fewer possibility of ADEs (intravenous, oral, topical and inhalation administration respectively), they can all potentially cause Adverse Drug Events (ADEs). Other routes of administration of corticosteroids are intra-ocular and nasal administration; these will be outside the realm of this study.

Due to their widespread mode of action, corticosteroids exert their effects on a wide array of tissues such as kidneys, cardiovascular system, endocrine organs, immune system and central nervous system as well as regulation of lipids, carbohydrates and proteins. In most instances, the ADEs are an extension of their pharmacologic properties and affect the same organs and tissues. The adverse effects of steroids are thought to be related to the dosage and duration of administration, although a dosing threshold is yet to be established for the development of ADEs.

ADEs may also be associated with the fact that release of endogenous steroids has been found to follow a circadian as well as ultradian (highly pulsatile) rhythm. This rhythm cannot be achieved by the continuous release following administration of synthetic steroids. In addition, synthetic steroids have a higher affinity for the GC receptor and a greater bioavailability than endogenous steroids. They are also poorly metabolised in comparison, and therefore tend to persist much longer in plasma.

Well recognized ADEs in adults include hypothalamic-pituitary-adrenal axis suppression; immune suppression and increased infections; impaired glucose tolerance and diabetes mellitus, Cushing’s syndrome, psychiatric disturbances; cardiovascular diseases and dyslipidaemias, osteoporosis; cataracts and glaucoma, dermatological and gastrointestinal disturbances.

At Kenyatta National Hospital, many of these newer and less toxic compounds such as biologic agents are far out of reach for the majority of patients, which translates to an even greater reliance on steroids. This means that corticosteroids are used at higher doses and for longer than in centres where steroid-sparing agents are available. In a retrospective audit carried out in 2011 at the KNH Rheumatology clinic on 394 patients, 54% of them were on corticosteroids. The commonest rheumatologic condition was Rheumatoid Arthritis (RA) which was present in 37% of the patients. Patients with Systemic Lupus Erythematosus (SLE) were only 9% and undifferentiated arthritis comprised 10%. Similar data from the other two clinics was not available.

In most instances, disease activity is high despite immunosuppressive therapy. Studies carried out in RA patients in the rheumatology clinic have shown high disease activity. In 2007, Owino et al. found that only 12% of the patients were in disease remission using DAS-28, 18% mild, 38% moderate and 32% high disease activity. In 2012, Mbuthia et al. found 11.5% of RA patients were in remission using DAS-28 (9.6% mild, 49% moderate and 29.6% high disease activity. Ganda et al. in 2012, using RAPID 3 tool found that 62% of the RA patients had moderate to high disease activity.

Data from the Kenya Association for the Prevention of Tuberculosis and Lung Diseases estimates that 4 million Kenyans (10-20% of the population) are living with bronchial asthma, majority of whom require inhaled and oral corticosteroids for control of the disease.

Common dermatological conditions encountered in our set-up include atopic dermatitis, contact dermatitis, seborrheic dermatitis, psoriasis and vitiligo. In majority of these conditions, topical and systemic steroids are instrumental in management of the conditions. Topical steroid exposure is measured in terms of percentage Body Surface Area (BSA) contact. In an adult patient, 100% BSA application of a topical steroid is approximated as an equivalent on 20mg of oral prednisolone.

Various guidelines exist internationally for evidence based management of corticosteroids ADEs. The European League Against Rheumatism (EULAR)15, the American College of Rheumatology (ACR)16, Canadian17 and South Africa18 have existing recommendations on glucocorticoid ADEs. Similarly, pharmacovigilance is a well-established tool for the surveillance of ADEs both locally19 and internationally20,21.

However, these guidelines have not been tailored specifically to address corticosteroid administration in our setting. This makes it imperative that this unique population of patients be assessed for Adverse Drug Events (ADE) and a surveillance protocol be put in place to recognize these complications earlier. Currently, there are no specific guidelines or job aids available in our clinics.
Studies evaluating the Knowledge, Attitudes and Practices (KAP) are useful in evaluating efficacy of a particular intervention. KAP studies in patients have shown less than optimum understanding of medications as well as their diseases. As self-care is the cornerstone in the management of chronic illnesses, it is imperative; therefore that continued education is carried out for optimization of care. Similarly, the KAP of health care workers has a direct correlation with good clinical outcome of patients. This study set out to establish the adequacy of knowledge among health care providers who were providing care to patients on chronic corticosteroid therapy.

Materials and Methods

This was a cross-sectional study carried out in June 2015 after approval from the University of Nairobi/Kenyatta National Hospital Ethics and Research Committee. Kenyatta National Hospital is the largest hospital in East and Central Africa and is located in Nairobi, Kenya. It serves as the largest teaching, tertiary and referral hospital in Kenya with a bed capacity of 1800 patients with over 6000 workers. Healthcare workers working in the ambulatory rheumatology, respiratory and dermatology clinics were recruited after giving written informed consent.

Study instrument: The questionnaire consisted of four sections and was open ended; the first section compiled demographic information, the second segment looked into knowledge of adverse drug events of steroids. The third section asked about other medications that may interact with corticosteroids to worsen the adverse drug events. The fourth section inquired about the advice patients receive about use of steroids. The questionnaire was distributed in paper formats to the HCWs for self-completion on the spot or to be filled and returned within one week of receiving the questionnaire.

Data analysis: Data collected was cleaned and entered into access data base and exported to SPSS 17.0 (Statistical Package for Social Sciences) for analysis. The answers provided were analysed by the investigators into total number of correct answers. Further analysis was done by grouping the correct answers into categories as per the systems affected by corticosteroids. A cut-off point of 5 correct answers was deemed adequate knowledge of ADRs. Correct answers given were calculated as a proportion of all the answers provided by the respondent. Median (interquartile range - IQR) was used to provide the midpoint of correct responses and the spread of the second and third quartiles respectively.

Results

Sixty two healthcare workers were recruited into the study with 28 (45%) of them having worked in more than one of the target clinics. Pharmacy personnel serving these three clinics were also recruited. Senior House Officers/Residents in Internal Medicine comprised of 66.1% of the respondents, with nurses making up 21% and pharmacy staff 12.9%. Majority (79%) had been stationed in the work-station of interest for more than one year.

Table 1: Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work station</td>
<td></td>
</tr>
<tr>
<td>Dermatology</td>
<td>36 (58.1)</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>8 (12.9)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>30 (48.4)</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>39 (62.9)</td>
</tr>
<tr>
<td>Cadre</td>
<td></td>
</tr>
<tr>
<td>Nursing officer</td>
<td>13 (21.0)</td>
</tr>
<tr>
<td>Pharmacists</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Pharmaceutical technologist</td>
<td>7 (11.3)</td>
</tr>
<tr>
<td>Senior house officer</td>
<td>41 (66.1)</td>
</tr>
<tr>
<td>Years of practice in station</td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>12 (19.4)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>3 (4.8)</td>
</tr>
<tr>
<td>&gt;5-10</td>
<td>7 (11.3)</td>
</tr>
<tr>
<td>1-5</td>
<td>36 (58.1)</td>
</tr>
<tr>
<td>Missing</td>
<td>4 (6.5)</td>
</tr>
</tbody>
</table>

Knowledge on adverse drug events of steroids known: The responses provided were grouped as shown in Table 2. Only 61% of HCWs were able to list 6 or more anticipated ADRs of corticosteroids. The median (IQR) of correct responses was 6.0 (3.0-9.5). Six correct answers were arbitrary used as the cut-off of adequate knowledge.

Table 2: Adverse drug events of steroids known

<table>
<thead>
<tr>
<th>ADRs</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic</td>
<td>55 (88.7)</td>
</tr>
<tr>
<td>Skin</td>
<td>38 (61.3)</td>
</tr>
<tr>
<td>Other</td>
<td>36 (58.1)</td>
</tr>
<tr>
<td>Bone</td>
<td>23 (37.1)</td>
</tr>
<tr>
<td>Gastro-intestinal system</td>
<td>22 (35.5)</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>20 (32.3)</td>
</tr>
<tr>
<td>Adrenal suppression</td>
<td>15 (24.2)</td>
</tr>
<tr>
<td>Myopathy</td>
<td>11 (17.7)</td>
</tr>
<tr>
<td>Eye</td>
<td>13 (21.0)</td>
</tr>
</tbody>
</table>

Knowledge on other medications that may interact with corticosteroids to worsen the ADRs: The knowledge of other medications that may interact with corticosteroids to worsen the ADRs was surprisingly low as shown in Table 3 as most answered less than 50%. The commonest drugs identified were NSAIDs (35%), Cytotoxics (34%) and anticoagulants (15%).
as corticosteroids are commonly used in the departments. Dispensing pharmacy was low. This is discouraging to note and looked for in these patients, the knowledge amongst the respondents said they advised on surveillance of ADRs with 48% counselling the patient on adhering to the dosage and duration of the drugs. Only 8% recommended that the patient should inform healthcare workers that they are on corticosteroids when they present to a health facility with only 1 respondent noting the importance on patients carrying a steroid card.

Knowledge on advice that should be given to the patients about use of steroids: When asked on instructions given to patients about the use of corticosteroids, 53% of the respondents said they advised on surveillance of ADRs with 48% counselling the patient on adhering to the dosage and duration of the drugs. Only 8% recommended that the patient should inform healthcare workers that they are on corticosteroids when they present to a health facility with only 1 respondent noting the importance on patients carrying a steroid card.

Table 4: What advice should be given to the patients about use of steroids?

<table>
<thead>
<tr>
<th>Advice</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance of ADR</td>
<td>33 (53.2)</td>
</tr>
<tr>
<td>Adhere to prescribed dosage &amp; duration</td>
<td>30 (48.4)</td>
</tr>
<tr>
<td>Tapering of steroids</td>
<td>20 (32.3)</td>
</tr>
<tr>
<td>Avoid over the counter corticosteroids</td>
<td>13 (21.0)</td>
</tr>
<tr>
<td>Advice on potential drug interaction with steroids</td>
<td>10 (16.1)</td>
</tr>
<tr>
<td>Drugs to prevent ADRs</td>
<td>8 (12.9)</td>
</tr>
<tr>
<td>Inform Health Care Worker (HCW) of concurrent steroid use</td>
<td>5 (8.1)</td>
</tr>
<tr>
<td>Should have a steroid card/tag</td>
<td>4 (6.5)</td>
</tr>
<tr>
<td>Rinse mouth after use of inhalational steroid</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Others</td>
<td>3 (4.8)</td>
</tr>
</tbody>
</table>

The median (IQR) for correct responses was 2.0 (2.0-3.0).

Discussion

Knowledge and attitude of HCWs on corticosteroids utility, safety and ADRs could greatly influence their behavior and thereby contribute to patient safety. It is important to assess these parameters so as to identify aspects that require actions or interventions from the various regulatory bodies. The present study is the first study of its kind in Kenya that has tried to assess the knowledge of health care workers on corticosteroids adverse drug events. Although the adverse drug events of corticosteroids are well known and should be anticipated and looked for in these patients, the knowledge amongst the healthcare providers working in these clinics and the dispensing pharmacy was low. This is discouraging to note as corticosteroids are commonly used in the departments surveyed for various conditions. These ADRs have a serious impact on both morbidity and mortality of those affected by them. An example of this is seen in a study by Oyoo et al\textsuperscript{26} where they reported that one in four of the patients with osteoporosis had been on a steroid.

It was discouraging to note that the knowledge on other drugs that could potentiate the ADRs of corticosteroids was low where about one third could identify NSAIDs or cytotoxic medicines. Majority of the patients served in these departments have comorbidities and are on polypharmacy so it is expected that the HCWs would know more about the drug interactions as this would influence their choice of medicines. We however did not inquire as to why the knowledge was low and what steps would the respondents suggest so as to improve their knowledge. This is a potential area for intervention.

More effort needs to be done on communication to the patient on corticosteroids from its usage, tapering, surveillance on potential ADRs etc as the number of positive responses was low. When asked on instructions given to patients about the use of corticosteroids, 53% of the respondents said they advised on surveillance of ADRs with 48% counselling the patient on adhering to the dosage and duration of the drugs. Only 8% recommended that the patient should inform healthcare workers that they are on corticosteroids when they present to a health facility with only one respondent noting the importance on patients carrying a steroid card. This is crucial as the usage of corticosteroids carries with it potential ADRs that can be prevented. Therefore, HCWs need to be actively involved in the surveillance of drug safety issues within the context of their practices. The role of the HCWs in pharmacovigilance may vary from country to country, but the professional responsibility is the same.

Limitations of the study

The results of this study should be considered within the context of its limitations. The sample size was small thus may lack true generalization.

Conclusion

The results of the present study showed that the majority of the HCWs working in the Dermatology, Respiratory and Rheumatology Departments at Kenyatta National Hospital have insufficient knowledge about corticosteroid ADRs. There is a need of pharmacovigilance in the Kenyatta National Hospital Pharmacy, under and postgraduate educational programs about corticosteroids ADR reporting and pharmacovigilance practice need to be included in the curriculum to improve ADR reporting.

Acknowledgements

To the health care workers who took part in the study and to research assistant Gladys Mwakio. Finally to Kenyatta National Hospital, Department of Research and Programs for funding the study.
References


Abstract

Systemic Autoimmune Rheumatic Diseases (SARD) are chronic disorders affecting multiple organs. Most SARDs have a female preponderance. SARDs have rarely been reported in African blacks, although there is increasing reportage of recent. Different SARDs are believed to have genetic predisposition and familial clustering. SARDs occasionally run in families - among mothers and daughters, among siblings. Such clustering has however not been documented among black Africans. We present four Nigerian families with clustering of systemic autoimmune rheumatic disease.

Key words: Systemic autoimmune disease, Familial clustering, Nigerians

Introduction

Systemic Autoimmune Rheumatic Diseases (SARD) are chronic autoimmune disorders affecting more than one organ. This group of disorders comprise Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Systemic Sclerosis, primary Sjogren’s syndrome, inflammatory myopathies and systemic vasculitides, among others. SARDs are being increasingly reported among black Africans2-3. This may be attributable to increasing awareness of these conditions among African physicians4. Its occurrence in more than one family member has been reported in literature, especially among female first degree relatives5,6. There have been reports of familial clustering from Japan Bangladesh and the USA7. There are no documented reports of such familial clustering in black Africans; hence this case series.

Family 1

Mrs JB, a 44-year old female presented with a 3-month history of alopecia, skin rashes and recurrent fever. She had multiple discrete lesions of scarring alopecia and atrophic lesions on both cheeks, bilateral pedal oedema, blood pressure was 110/60mmHg.

Investigations: Erythrocyte Sedimentation Rate (ESR) - 63mm/hr, proteinuria 3+. Urea and creatinine were normal. Antinuclear Antibody (ANA) - positive, (titre of 1:2,560; speckled pattern), anti-double stranded DNA antibody was positive. A diagnosis of SLE, with lupus nephritis was made - using the 1997 ACR criteria for SLE7. She was pulsed with intravenous methylprednisolone (500mg daily for 3 days), then continued with oral prednisolone (40mg daily, tapered over weeks), azathioprine and hydroxychloroquine. During one of her follow up visits, she mentioned that her daughter had deformed hands.

Her daughter, Miss JR, was 27 years old, and presented with a two-year history of pain in all joints of both hands. There was associated history of morning joint stiffness, swelling and deformities. Physical examination revealed swelling of all the Proximal Interphalangeal (PIP) joints of both hands and ulnar deviation at the PIP joints (Figure 1).
Rheumatoid Arthritis (RA) was made. She was managed with triple therapy, folic acid and low dose prednisolone.

**Figure 2:** Oblique radiographs of both hands (Daughter, Family 1)

**Figure 3:** Posteroanterior radiographs of both hands (Daughter, Family 1)

**Family 2**

Mrs AO, a 58-year old female presented with a 5 year history of pain in the joints of her hands, wrists and ankles. There was a history of joint swelling with early morning joint stiffness lasting longer than 2 hours. Physical examination revealed swelling and tenderness of her wrists, MCPs, PIPs and ankle joints. Chest examination revealed crepitations in the middle and lower zones of both lungs.

Investigations: Elevated C-Reactive Protein (CRP) -71.6mg/L, anti-CCP - 94.0 EU/ml (ref: 0-30.0), RF - negative. Radiographs of both hands showed generalised osteopaenia of all the bones of the hands, narrowing of thePIP joints of the 2nd and 3rd digits bilaterally, and erosions in the first MCP joints. There was also subluxation of the MCP and PIP joints bilaterally and erosion of the medial part of the right ulnar bone. A chest radiograph showed bibasal alveolar filling opacities, mild cardiomegaly with left ventricular preponderance. The features were in keeping with pulmonary interstitial fibrosis.

An assessment of rheumatoid arthritis with interstitial pneumonitis was made. She was placed on hydroxychloroquine, sulphasalazine and prednisolone (which she took haphazardly). Her Clinical Disease Activity Index (CDAI) at the start of treatment was 35.0. She was changed to etanercept as her CDAI remained high even after one year. This was at a dose of 50mg weekly, but could only be given for 3 months because of financial constraints. She was subsequently lost to follow up, and was reported to have died from features suggestive of a myocardial infarction in another hospital 4 months later. Her daughter, Mrs OO, was 34 years old and presented 2 months after her mother died. She had a history of polyarthritis (wrists, knees and ankles) which started 3 months post-partum. She also had a history of fever, weight loss, and pedal oedema. On physical examination, she had synovitis of her wrist joints, both knees and ankles, and pitting pedal oedema extending up to both mid-thighs. Other systems were essentially normal.

**Investigations:** Haematocrit - 19%, ESR of 95mm/hr, dipstick urinalysis with 3+ proteinuria, 4+ haematuria, urine protein/creatinine ratio was 3.455g/g (reference range: 0.0-0.15). RF and anti-CCP both - negative, ANA positive (titre-1:640), Extractable Nuclear Antigen (ENA) screen –positive- at a level of 25.0 (reference range: 0.0-0.7). A diagnosis of lupus nephritis was made. She was pulsed with intravenous methyl prednisolone (500mg daily for 3 days) and thereafter commenced on intravenous cyclophosphamide (Eurolupus regimen). She is presently on mycophenolate mofetil.

**Family 3**

Miss OP, a 34-year old female - presented with a 3 year history of pain in the joints of her hands, elbows, shoulders and knees, with associated joint stiffness. She also had a previous history of a photosensitive rash, recurrent oral ulcers, and seizures. Physical examination revealed submandibular lymphadenopathy, tachycardia and bilateral loin tenderness.

Investigations: ANA- positive (titre 1:160, speckled pattern), anti-Sm antibody-positive, anti-nRNP antibody-positive, dipstick urinalysis - 1+ proteinuria.

An assessment of SLE was made and she was placed on hydroxychloroquine and prednisolone. Six years later, she had a left hemispheric CVD, with right-sided hemiparesis. Anti-phospholipid antibodies were normal. Subsequently, on account of persistently high disease activity, azathioprine was added to her drug regimen. She is still being followed up.
Her younger sister, Mrs TR, was a 30-year old female who presented with a 2 year history of joint pain and swelling in the fingers of both hands, and early morning joint stiffness. On examination, she had subcutaneous nodules on the extensor aspects of both elbows, synovitis of the PIP joints of the 3rd and 4th digits of the right hand, and tenderness in her shoulders, elbows, wrists and knees.

**Investigations:** ESR 46mm/hr, RF72.9 IU/ml, anti-CCP 693 EU/ml. An assessment of RA was made and she was commenced on methotrexate, folic acid, and prednisolone. She is currently stable with low disease activity (CDAI-8.0) on this regimen.

**Family 4**

Mrs FO was a 32-year old woman who presented with a 6-month history of polyarthritis involving the joints of her shoulders, elbows, hands and ankles. There was associated joint morning stiffness lasting more than 1 hour in addition to dry eyes and dry mouth. On examination she had synovitis in all her MCP and PIP joints. She also had bilateral parotid enlargement.

**Investigations:** ESR-120mm/hr, CRP-15.5mg/L, ANA - positive (titre-1:640), Anti-SSA and Anti-SSB-positive, RF-marginally positive (23.6 IU/ml). Anti-CCP - negative (0.6 U/ml).

An assessment of Sjogren’s syndrome was made, and she was commenced on methotrexate, prednisolone, folic acid, pilocarpine and hydroxychloroquine. She has had occasional flares and is presently on hydroxychloroquine. Her daughter, Miss CO, presented at 10 years with a history of polyarthralgia, passage of frothy urine and recurrent fever. On examination, she was febrile and had tenderness in her right knee and left ankle.

**Investigations:** Hct-30%, WBC-3.90 x 10^9/L (N-75%, L-25%), Platelets-283 x 10^9/L. ESR-90mm/hr.

**Urinalysis:** protein-2+, RBC-11-20/hpf, epithelial cells>10, specific gravity-1.030, pH-7.0. ANA was positive (titre-1:640), anti-dsDNA-negative. An abdominal ultrasound scan revealed Grade II renal parenchymal disease. An assessment of juvenile SLE was made. She was commenced on mycophenolate mofetil, prednisolone, calcium lactate, hydroxychloroquine and folic acid. She is stable, with low disease activity on this regimen.

**Discussion**

These cases are presented to illustrate the familial clustering of SARD in black Africans. There were three mother-daughter cases (mother with SLE, daughter with RA; mother with RA, daughter with SLE; and mother with Sjogren’s syndrome, daughter with juvenile SLE). The fourth family comprised of two sisters (one with SLE, the other with RA). The family characteristics are shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1: Family characteristics</th>
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<tbody>
<tr>
<td>First generation</td>
</tr>
<tr>
<td><strong>Family 1</strong></td>
</tr>
<tr>
<td><strong>Family 2</strong></td>
</tr>
<tr>
<td><strong>Family 3</strong></td>
</tr>
<tr>
<td><strong>Family 4</strong></td>
</tr>
</tbody>
</table>

There is increasing reportage of SARDs among black Africans, contrary to previously held notions that these conditions were rare. There have been reports elsewhere of familial clustering of SARD: SLE in both mother and son in Japan, scleroderma in two members of the same family in Bangladesh, and juvenile dermatomyositis occurring in brother and sister in the USA.

It is believed that there are genetic predispositions to the occurrence of autoimmune disease as these diseases tend to cluster in families. Ramos et al have observed that the genetic overlap between SLE and other autoimmune diseases was however modest. It has been noted that there is an association of RA amongst the family members of patients with SLE. As noted in this case series, 3 of the families had SLE in one member, and RA in another. It is believed that there is a familial aggregation of SLE and RA which could be due to the action of genes which predispose individuals to developing autoimmune disease. Such genes include PTPN22, CTLA4, STAT4 and TNFAIP3 which predispose to both SLE and RA.

In a study to determine whether transmission of SLE or RA from a parent to child was dependent on the sex of either party, it was documented that female offsprings are at greater risk of manifesting SARDs than their male counterparts. There was no male subject among any of our cases.

**Conclusion**

We have presented four families which clearly demonstrate familial clustering of SLE and RA, and SLE and Sjogren’s syndrome. It could be postulated that these patients have a genetic predisposition to these autoimmune diseases (SLE and RA).
References


Acosmetologist with systemic sclerosis

Ojo O, Omosore-Bakare M, Davidson B

Abstract

Scleroderma is a rare disease. This case report highlights its occurrence in a cosmetologist raising the possibility of exposure to organic solvents as a cause as well as the myriad of clinical presentations in such patients. The diagnosis was made using the 2013 ACR/EULAR classification criteria for scleroderma. The essential features were those of widespread hypo and hyperpigmented ('salt and pepper') skin lesions, healed digital ulcers, proximal myopathy, gastrointestinal manifestations, extensive skin fibrosis and tendon friction rub. She tested positive to anti nuclear antibodies with a nucleolar pattern and antibodies to Scl-70 was positive. Her lung function test revealed a restrictive pattern.

Keywords: Scleroderma, Cosmetologist, ‘salt and pepper appearance’

Introduction

The first convincing description of scleroderma was in 1753 by Carlo Curzio. He described a 17 year old patient as having ‘extensive tension and hardness of skin all over her body’. It was in the mid 19th century that scleroderma was established as a clinical disease entity and given its current name.

It is a rare autoimmune connective tissue disease of unknown aetiology characterized by thickening of the skin caused by accumulation of collagen and by injuries to the smallest arteries. A myriad of factors such as genetic, environmental, vascular, autoimmunologic and microchimeric factors are involved in its pathogenesis. According to the 2013 ACR/EULAR classification criteria for scleroderma, skin thickening of the fingers extending proximal to the metacarpophalangeal joints is sufficient for a patient to be classified as having scleroderma. If this is not present, seven other additive items are considered, with varying weights for each. This includes finger tip lesions, telangiectasia, abnormal nail fold capillaries, pulmonary hypertension and/or interstitial lung diseases, Raynaud’s phenomenon and serological markers such as anticientromere, anti-topoisomerase 1 and anti-RNA polymerase 3 antibodies. Patients with a total score of ≥ 9 are classified as having definite scleroderma.

The incidence and prevalence of Systemic Sclerosis (SSc) varies in different populations. It seems to be more prevalent in United States (276 cases per million adults), than in Europe (8-15 cases per million adults). The annual incidence of new cases has been reported as 1 to 20 cases per million. It is three times more common in women than in men. The higher incidence of scleroderma among blacks has been attributed to the postulation that in this ethnic group certain connective tissue responses which are involved in protection against infection and repair after injury may also predispose to certain diseases.

Environmental factors could be classified as occupational (silica, organic solvents), infectious (bacterial, viral), and non-occupational/non-infectious (drugs, pesticides, silicones). Exposure to silica through various occupations remains one of the main environmental risk factors for SSc. Other occupational agents, such as epoxy resins, welding fumes and hand-arm vibration, have been investigated, but no definitive associations may be made due to small sample sizes.

Solvents are liquids that dissolve a solid, liquid or gas. Organic Solvents (OSs) are compounds whose molecules contain carbon. Common uses for OSs are: dry cleaning (e.g., tetrachloroethylene), paint thinner (e.g., toluene, turpentine), nail polish removers and glue solvents (acetone, methyl acetate, ethyl acetate), spot removers (e.g., hexane, petrol ether), detergents (citrus turpenes), perfumes (ethanol), nail polish and chemical synthesis. Rein was the first to point out the association between systemic sclerosis and exposure to solvents.
Exposure to certain organic compounds such as vinyl chloride monomers, trichlorethylene, benzene, and other solvents has been reported as a risk factor of SSc in case reports and in two case-control studies\textsuperscript{11, 12}. A meta-analysis published by Aryal \textit{et al}\textsuperscript{13} confirmed a significant positive association between exposure to solvents and systemic sclerosis.

Marie \textit{et al}\textsuperscript{14} in a study on environmental risk factors for SSc noted a marked correlation has thus been found between SSc onset and occupational exposure to crystal-line silica and the following organic solvents: white spirit, aromatic solvents, chlorinated solvents, trichloroethylene, and ketones.

Based on the rarity of this disease, we report a case highlighting its multisystemic presentation and its occurrence in a cosmetologist.

\textbf{Case report}

The patient was a 34 year old single lady who was in stable health until 18 months prior to initial presentation when she noticed skin discoloration involving her right hand. She subsequently developed swelling of both feet and face. The facial swelling was worse in the mornings. There was an associated history of difficulty with breathing on activity but not at rest. There was subsequent affectation of the skin of the face, ears, neck, chest, upper and lower limbs as well as multiple joint pains. She experienced early morning stiffness of an hour’s duration. She had digital ulcers which healed leaving atrophic scars. This also involved the dorsal aspects of the proximal interphalangeal joints of the middle digits. She did not experience Raynaud’s phenomenon. She complained of occasional fatigue, pruritus, difficulty with standing from a sitting position as well as difficulty with lifting her upper limbs. She had no history of hair loss, oral ulcers or difficulty with swallowing but experienced epigastric pain which radiated to the back. She has had recurrent diarrhoea alternating with constipation with occasional fecal incontinence. She was a cosmetologist who had been in business for a year before onset of symptoms. She was involved in hair fixing, nail polishing, fixing or removal which led to exposure to organic solvents such as benzene sulphate, cholesterol tea-tree oil, olive oil hair mayonnaise, phenoxyethanol, polyanionic cellulose, isopropyl alcohol and propylene glycol. No history of use of botulinum injection for her clients.

Essential examination findings were widespread hypo and hyperpigmented (‘salt and pepper’) skin lesions on the face, trunk and limbs (Figure 1). She had bilateral pitting pedal edema up to the distal third of the legs and microstomia.

\textbf{Discussion}

The reported case met the ACR/EULAR 2013 criteria\textsuperscript{3} for definite systemic sclerosis. Systemic sclerosis is subdivided into limited cutaneous scleroderma and diffuse.
cutaneous scleroderma. Limited cutaneous scleroderma affects the skin, the fingers, hands, face, lower arms, and legs and may present with CREST syndrome (Calcinosis, Raynaud’s phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasia). In diffuse cutaneous scleroderma, skin thickening begins in the hands with subsequent involvement of the face, upper arms, upper legs, chest with internal organ affection such as the lungs, kidneys, stomach and intestines. The higher frequency of the diffuse form in blacks is confirmed by the index case as well as increased occurrence of anti topoisomerase15. The female preponderance seen in other reports is highlighted in this case as well as the younger age at presentation amongst blacks. The patient was aged 34 years as against 36.1 years in the series by Tikly et al16 and 51.5 years among Caucasians17. She had features suggestive of proximal myopathy. Muscle weakness is a significant problem in SSc and often has more than one cause18. A myopathy can occur from a direct extension of the fibrosis into the muscle itself in which case the patient presents with weakness, fatigue with mildly elevated creatine phosphokinase and abnormal electromyography19. The patient had a history of digital ulcers with healed atrophic scars (Figure 2). She however did not report having Raynaud’s phenomenon which is rarely reported in Black Africans20. There was a co morbidity of peptic ulcer disease as well as constipation alternating with diarrhoea and fecal incontinence. Gastrointestinal tract involvement is almost universal in patients with systemic sclerosis and is characterized by abnormal motility secondary to dysfunctions caused by abnormal innervations, smooth muscle atrophy and tissue fibrosis21. In a study conducted to determine incidence of gastrointestinal manifestations in patients with systemic sclerosis, Wielosz et al22 reported that gastrointestinal (GI) symptoms were observed in 74% of patients and that upper GI symptoms were observed in 54 (74%) patients and lower GI symptoms in 22 (30%) patients.

She had florid cutaneous manifestations: the ‘salt and pepper’ appearance, hide bound skin as well as flexion contractures of the digits as well as the elbows. Skin thickening typically peaks in the first 3 to 5 years23. This is within the time frame the patient presented and also accounts for the contractures at the digits and elbows.

The patient had microcytic anaemia. Elkayam et al24 reported two patients with systemic sclerosis who presented with microcytic hypochromic anaemia and were found to have watermelon stomach. This could have accounted for the iron deficiency anaemia and its manifestations such as fatigue. A positive anti nuclear antibody with a nucleolar pattern is in consonance with a similar finding amongst three of the nine tested patients in a study by Adelowo et al20. The presence of antibodies to topoisomerase correlates with the clinical finding of the diffuse type and the presence of interstitial lung disease.

The aetiology of systemic sclerosis is unknown. However evidence suggests the role played by environmental factors13. Exposure to organic solvents such as benzene might have predisposed her to this condition. Further studies will be required to determine a causal relationship.

Conclusion

Systemic sclerosis is a rare disease. Exposure to organic solvents may trigger the disease in a genetically susceptible individual. The limitations here include unavailability of facilities to carry out investigations such as nailfold videocapillaroscopy as well as the cost of investigations taking into cognizance the fact that most patients are not covered by health insurance and so bear the cost of management.

References

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