



Haematological variables in rheumatoid arthritis patients in Imo state Nigeria

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Abstract

The effects of rheumatoid arthritis on some haematological variables were determined. A total of one hundred and fifty six (156) subjects were recruited for the study. Seventy (70) Subjects were females suffering from rheumatoid arthritis and seventy (70) subjects were apparently healthy females. Eight (8) subjects were males suffering from rheumatoid arthritis and eight (8) subject were apparently healthy males Full blood count, erythrocyte sedimentation rate platelet count of sufferers, and non-sufferers who served as control were determined using standard haematologic methods. t-test analysis revealed significant statistical differences in all variables ($P < 0.05$), except lymphocytes and monocytes in male arthritics. Anaemia, leukaemia and thrombocytopenia were seen in some percentage of patients, Haematologic surveillance in rheumatoid arthritis disease, and instituting rheumatoid arthritis disease management programme will assist in reducing complications that may be brought about by haematologic changes and ignorance.

Keywords: Rheumatoid arthristis, Haematological Variations, Full Blood Count, Erythrocyte Sedimentation Rate.

Introduction

Rheumatoid arthritis is a chronic inflammatory disease characterized by severe-pain, swelling, stiffness and loss of function of the joint (Bengteson et al., 2005). It is classified as autoimmune disease characterized by deregulation of the immune system, resulting in Chronic activation of T – cell responses and over production of proinflammatory cytokines including tumour necrosis factor and interleukin 1 (Reischmann et al., 2005). It is classified as autoimmune disease characterized by deregulation of the immune system, resulting in Chronic activation of T-cell responses and over production of proinflammatory cytokines

including Tumour necrosis factor and interleukin 1 (Fleischmann et al., 2005).The resultant effect of the above response is joint destruction.

The precise cause of RA is not known (Edward et al., 2006) disease models suggest that both genetic, environment and hormone are contributing factors. Firestein, in his publication classified the aetiology of RA as genetic, environment, hormone and socio - economic status.It has been reported that genetic make up of an individual plays an important role

in determining the susceptibility of the person to developing rheumatoid arthritis.

High rate of concordance between monozygotic twins and a ill-defined familial disposition has been reported (Silman et al., 1993) the association of human leucocyte antigen and DR4 with RA is well documented. There is an increased human of RA with this allele (Warrington et al., 2001). Many researchers have come to the conclusion that some environmental factors trigger the disease process in the people whose genetic make up makes them susceptible to rheumatoid arthritis. There has been limited success in defining these factors, but recent work has suggested prenatal characteristics as important in the development of rheumatoid arthritis (Jacobson and Jacobson, 2003). Infectious agents have long been suspected as potential triggers of RA. Researchers have not been able to identify any organism in the synovial tissue or bacterial nucleotide sequence in synovial tissues of RA patients (Kathleen et al., 2004). Viral pathogens are still being studied with Epstein Barr virus targeted for some reasons: RA patients have been found to have high levels of Epstein Barr virus antibody titers than non RA subjects (Charles, 2005). In addition, the ability of the virus to activate B cells to produce rheumatoid factors has generated interest in this virus as a potential trigger in RA (Gerard et al., 1998). The possibility of bacterial and viral antigenic particles being carried to the site gut-associated macrophages has been reported. Association between environmental factor during infancy and RA has equally been reported. It was suggested that early exposure to infectious micro-organisms during infancy may predispose one to RA during adult life (Edward et al., 2006).

Some scientists have suggested that a variety of hormonal factors may be involved in RA. The presence and activity of a number of proinflammatory chemokines and cytokines have established roles in disease pathogenesis. The activation and infiltration of T cells and macrophages in the synovium result in the production of interleukin -1, -2, -6, -8 and 10, transforming growth factors Beta (Goronzy, 2004). These infector molecules are implicated in synovial tissue inflammation as well as having systemic effects on B cells, also infiltrate the synovium and differentiate into plasma cells, producing polyclonal immunoglobulin and activating metallo proteinase gene expression which leads to destruction of matric tissues. This may result in pannus formation with articular cartilage inversion particular erosions,

osteoporosis and joint swelling as well as destruction of particular structure (Bingham, 2002).

A low social class has been associated with a worse tical out come in RA (Symmons, 2003). Social class according to occupation in relation to rheumatoid arthritis has in observed (Padyukov et al., 2004).Low formal education been found to be associated with increased risk of iritis including RA. (Krishman et al., 2003).It was reported that women as well as men with formal location or working as higher non-manual employees had a >wer risk of developing rheumatoid arthritis (Bengtsson et al.,2005).Cigarette smoking increases the risk of developing RA md negatively influences diseases course (Stolt et al., 2003).

The earliest changes recorded in RA are swelling of the ial membrane and the underlying connective tissue. The synovium becomes infiltrated with lymphocytes especially ilper T cells, plasma cells and macrophages (Blab et al., 1999). Effusion of synovial fluid into the joint space takes place the active phase of the disease.Subsequently, hypertrrophy of the synovial membrane occurs with the lation of lymphoid follicles resembling immunologically lymph node.Inflammatory granulation tissue (pannus) is led spreading over and under the articular cartilage which is iressiveiy eroded and destroyed (Firestein, 2001).This is followed by fibrous adhesion which may form between the ;rs of pannus across the joint space and fibrous ankylosis occur in muscles adjacent the inflamed joint atrophy. There is a central area of fibrinoid material consisting of swollen and fragmented collagen fibers,fibrinous exudates and cellular debris.The nodule is surrounded by a loose capsule of fibrous tissue. Similar granulomatous lesion may occur in the pleura lung pericardium and sclera lymph nodes are often hyperplastic showing many lymphoid follicles with large germinal centre and numerous cells in the sinuses of medullary cords.Immunofluorescence shows that the plasma cells in the synovium and lymph node synthesize rheumatoid factors.

The onset of RA is insidious in majority of cases with joint pain, stiffness and symmetrical swelling of a number of peripheral joint (Brandtzaeg, 1997). Initially pain may be experienced only on movement of joints, but rest pain and especially early morning stiffness is characteristic of active RA. In the typical case the small joints of the fingers and toes are the proximal interphalangeal joint which gives the fingers a spindled appearance and swelling of the

metacarpophalangeal joints resulting in broadening of the fore foot (Lipsky and crush, 1998).As the disease progresses with or without remission, it may spread to the wrist, elbows, shoulders, knees ankles, subtalar and metatarsophalangeal joints. The hip joints are affected only in the more severe cases, but, neck pain and stiffness from cervical spine involvement is common (Kelly et al., 1999). As disease progresses, pain, muscle spasm and progressive joint destruction which may cause limitation of joint motion takes place.Joint instability,subluxation and deformities may occur, which could be corrected at first but later permanent contratural develop and joint many become completely disorganized (McCarty and koopman 1993). This may result to anorexia, weight loss, lithergy and myalgia. Extra articular features include: Raynaud's Phenomenon. Lymphadenopathy, osteoporosis and many others (Gronzy, 2004).

Ocular manifestations include: Keratoconjunctivitis sica or dry eyes syndrome. This has been reported in 15 - 25 percent of patients. Others include scleritis or episcleritis which has been recorded in 4 to 10 percent of RA patients (Harper and Foster, 1998).

Cardiovascular manifestation may include asymptomatic pericarditis and rarely pericardial effusion vasculities may also manifest and presents as leucocytoclastic which may occur as Isolated skin finding with less common medium sized involvement. Pulmonary manifestations in RA is mainly interstitial lung disease. Patients with severe RA or those who smoke are more likely to develop RA associated interstitial lung disease.

The most common haematologic manifestations of RA is mild anaemia with haematocrit values in the range of 30 - 34 percent. This has been recorded in 25 - 35 percent of patients. It is characterized by low concentration of serum -iron and low serum iron binding capacity and does not respond to oral iron. The chronic anaemia may be complicated by true iron deficiency secondary to gastrointestinal blood loss from those treat with analgesic and anti inflammatory drugs (Denesi and Taccam,2004).

White blood cells may be within the normal range or slightly elevated, but high counts has been recorded by past researchers. Increase in neutrophils has equally been recorded as well as raised basophil counts (Harrison, 2001).Leucopenia though very rare could be observed in a chronic state. There may be a shift to the left in neutrophilia. Eosinophilia has been reported in most studies.

By all measures, the financial and social impact of all types of arthritis including rheumatoid arthritis is substantial, both for the nation and individuals (Hallert et al., 2004).Economically,the medical and surgical treatment for rheumatoid arthritis and the wages lost because of disability caused by the disease add up to billions of dollars annually.

The total economic impact of RA in England was estimated at 1.2556 billion pounds due to production loss caused by RA disability (McIntosh, 1996). Daily joint pain is an inevitable consequence of the disease and most patients experience some degree of depression and feeling of helplessness. For some people RA can interfere with normal daily activities, limit job opportunities, or disrupt the joys and responsibilities of family life (Kevin, 2004).The excess mortality rate associated with RA has changed according to research work by (Gabriel et al., 2000).In recent analysis, the most common causes of death in patients with RA in the United State were cardiovascular, cancer and infection (Pincus,2004).

Materials and Methods

Study area

Imo state lies in the tropical rainforest belt of South Eastern Nigeria. It is made up of 27 local Government areas and has projected population of 3.4 million people. The people enjoy two distinct seasons; the rainy season which starts in May and ends in October with annual rainfall of 222.2mm and high relative humidity of 78 percent while the dry season begins in November and ends in April with high temperature of 22.0°C. The topography of the state remains flat land around Owerri zone and some adjoining local government areas from other zones (Orlu and Okigwe). It is surrounded by neighboring states like Abia, Anambra, River, Enugu, Akwa-Ibom and Cross River. The people accommodate immigrants from all over the world. The people of Imo state are served by 28 government owned hospitals and many private ones.

Study population

A total of one hundred and fifty six (156) subjects were recruited for the study.Seventy (70) Subjects were females suffering from rheumatoid arthritis and seventy (70) subjects were apparently healthy females.Eight (8) subjects were males suffering from rheumatoid arthritis and eight (8) subject were apparently healthy males.Screening of subjects was

based on their clinical presentations; hospital records, oral interviews and relevant laboratory Investigations. Haematological variables determined were haemoglobin level, packed cell volume, total and differential white cell count, platelet count, and erythrocyte sedimentation rate and blood picture.

Ethical consideration:

Consent were obtained from the research and ethic committee of the health institution used for the study who gave approval for the research work and informal consent obtained from patients or their relations as well as nurses and physicians in charge of the wards.

Specimen collection

Blood

The subjects were made to sit comfortably. The antecubital vein of the upper arm where the blood was to be collected was sterilized with 70% alcohol soaked on a cotton wool. A rubber tourniquet was applied around the upper arm, 5.5 milliliter of blood was drawn from the vein and distributed as follows:- 1.5mls of blood was delivered into a uric acid oxalate bottle, 2.5mls into ethylene diamine tetracetic acid (EDTA) bottle, 1ml into a bottle with paper clips where necessary and 0.5mls was put in a dry tube and allowed to clot.

Detection of rheumatoid factor

Tie latex slide of costa was used. The antigen, a particulate latex suspension coated with human gamma globulin, agglutinates in Rheumatoid factors in the patients serum, Procedure: The test reagents and sample was brought to room temperature. A drop of the sample and 1 drop of control were placed on the circled test card. The rheumatoid factor latex reagent was added to the circle on the card where the sample to be tested was put. The two mixtures were mixed with a disposable stirrer and spread over the entire area enclosed by the ring.

The card was rotated at 100 rpm for 2 minutes. The presence or absence of visible clumps determined whether the test were positive or negative. The presence of visible agglutination indicates a content of rheumatoid factor 30 /u/mz.

Haematological variables Haemoglobin estimation

The Cyanmethaemoglobin method was used. When anticoagulated blood is diluted in buffered solution of

potassium ferricyanide and potassium cyanide, the potassium ferricyanide converts the haemoglobin to methaemoglobin which is further converted to Cyanmethaemoglobin by the action of potassium cyanide. This produces a coloured solution whose absorbance is read in a colorimeter at a wavelength of 540nm. The optical density of the mixture is directly proportional to the concentration of the Haemoglobin present in it.

Procedure

5mls of drabkin solution were added to 0.02ml of well mixed EDTA blood using clean haemoglobin pipette. The contents were mixed properly by inversion and allowed to stand for 10 minutes for full colour development. The mixture was then transferred into cuvette and was read at 540nm, using the Drabkin reagent as blank.

The haemoglobin values obtained were read from a standard haemoglobin calibration curve. Haemoglobin concentration (g / dl) = A of blood sample x Conc. Of Std. x D.F

A of Std.	.	1000
A	=	Absorbance
Std.	=	Standard
D.F	=	Dilution Factor.

Haematocrit estimation:

The microhaematocrit method was used as described by Dacie and Lewis, (2001).

When anticoagulated whole blood is centrifuged in a capillary tube, there is packing of the red cells and the space occupied by the packed red cells is measured and expressed as a percentage of whole blood volume.

Procedure

1. A plain, non-graduated capillary tube of about 7cm in length and 1 mm bore diameter was filled with a properly mixed EDTA blood by capillary action. Two capillary tubes were filled for each sample up to about 3/4 from the upper end.
2. The filled end of each tube was properly sealed using a plastic seal. The tubes were placed in the radial grooves of the microhaematocrit centrifuge, spun for 5 minutes at 12,000 revolution per minutes (rpm).
3. The value of the PCV was obtained using the microhaematocrit reader.

Total leucocyte counts:

Standard method of total leucocyte count was employed. Red cells were lysed when whole blood were diluted in Turks Solution of 1% glacial acetic acid. The white cells remain intact their nuclei stained deep violet.

Procedure

To 0.38ml of Turk's solution in a glass test tube, 0.02ml of EDTA anticoagulated blood was added.

The mixture was thoroughly mixed by rotation for about 1 minute.

The chamber was cleaned and the cover slip firmly applied.

The chamber was charged and was allowed to settle for one minute for proper settling of the cells.

Leucocytes count was done in the four corners of the counting chamber using the lower power (10 x eye piece lens) and 16mm objective lens. The value obtained was multiplied by 50 to obtain the total leucocytes count (1st principle).

Differential white cell count

These were done by visual examination of blood film on a slide by the spread technique (Cheesbrough, 2004).

Procedure: Plain microhaematocrit tubes were used to drop well mixed EDTA blood onto the surface of clean glass slides at about 1cm from the end.

Placing the slides on a smooth surface thin film of about 2cm long was made using the spreader.

Film staining

Procedure

Prepared thin films were flooded with Leishman's stain for 2 minutes.

Equal volume of buffered distilled water (PH 6.8) was added and mixed by gentle rocking. The diluted stain was allowed to stand for 10 minutes.

The films were washed with buffered solution until the appearance of a Salmon pink colour of red cells were observed.

Films were drained and dried in the air at room temperature, the back of the slide were cleaned and then set for examination.

The stained blood films were inspected microscopically using, x20, X 40, objectives for general survey and oil immersion objective (x 100). The cells were counted in a strip running the whole

length of the film. The films were inspected using the longitudinally until all the cells were counted.

Erythrocyte sedimentation rate (ESR):

The Westergreen method was used as described by (Cheebrough, 2004).

When anticoagulated blood is left to stand undisturbed for 1 hour the red cells sediment gradually to the bottom of the tube leaving clear plasma on top and the distance occupied by the supernatant plasma is determined.

Procedure

The blood samples were mixed thoroughly and drawn up into a westergreen tube to a 200mm mark using teat. The blood samples were mixed in the proportion of 0.4mls of trisodium citrate to 1.6mls of EDTA blood.

The tubes were allowed to stand vertically undisturbed for 60 minutes. The height of the clear plasma above the upper limit of the column of sedimented cells were read to the nearest Imm. The result expressed as mm/hour.

Platelet count

Red cells were lysed when blood was diluted in 1% ammonium oxalate solution. The platelets remain intact.

Procedure

0.38mls of ammonium oxalate solution was mixed with 0.02mls of EDTA blood. The counting chamber was charged as in leucocyte. The four corner center square and one at the center were counted after 20 minutes of allowing the cells to settle in a wet petri dish.

Calculation = cells counted x 20 x 10⁶
0.2 x 0.1
20 = dilution factor
0.2 = area of the chamber
0.1 dept of the chamber.

Data analysis

The data generated were analyzed statistically, using prevalence rate and student t-test to ascertain prevalence of each of the diseases and the interaction of sex and age as well as level of significant between the sufferers and non sufferers.

Table 1 :Haematological values in female arthritics as compared with non-arthritic females

:	ARTHRITIC		NON-ARTHRITICS		TEST STATISTICS (t
	Mean ± SD		Mean	+ SD	P
parameters					
Haemoglobin	9.6 + 1.3		12.2	±0.6	<0.05
PCV%	29.0 ±3.5		36.9	±2.0	<0.05
WBCx 10 ⁹ /l	3.9 ±1.3		5.4	±1.1	<0.05
Platelet x 10 ⁹ /l	179 ±31.9		267	±46.0	<0.05
ESR per hour	67 ±16.3		7.5	±2.8	<0.05
Neutrophil %	55 ±8.0		65.5	±6.1	<0.05
Lymphocytes %	41 ±7.6		32.6	±6.5	<0.05
Eosinophil %	1±1.6		1.1	±1.2	<0.05
Monocytes %	1 ±1.0		0.7	±0.9	<0.05
Basophils %	-		-	-	—

Sample size (N) = 140

Table 2 :Haematological values in male arthritics as compared with non-arthritic males

parameters	ARTHRITIC FEMALES		NON-ARTHRITICS		TEST STATISTICS (t TEST)
	Mean	±SD	Mean	± SD	P.
Haemoglobin	9.8	±1.2	13.2	±0.9	<0.05
PVC(%)	31.6	±3.7	38.8	±3.5	<0.05
WBC (x 10 ⁹ /L)	3.5	±1.4	5.8	±1.0	<0.05
Platelet(x 10 ⁹ /L)	172.5	±20.4	225	±54.1	<0.05
ESR (per hour)	73.2	±17.5	5.4	±3.1	<0.05
Neutrophil(%)	53.0	±3.9	3.9	±9.3	<0.05
Lymphocytes(%)	41.3	±5.3	34.4	±9.3	<0.05
Eosinophil(%)	4.0	±1.5	0.8	±1.0	<0.05
Monocytes(%)	1.0	±0.7	0.4	±0.6	<0.05
Basophils(%)	—	—	—	—	I

Sample size (N) = 16

Discussion

The most important aspect of results obtained from this study were the variations in haematologic variables determined. In RA females, as recorded in table 1, all the haematologic variable determined except basophil, had significant statistical difference from the control values (P<0.05).

It was equally discovered that 80% of the subjects had haemoglobin below 11.Ig/dl. 60% had white cell count of below 4.0-10.0x10⁹/L and 10% had platelet below 150x10⁹/L. The values obtained deviated from documented normal values for elderly Nigerians by Nkeiru et al. (2004) and those of normal Nigerian values. Similar unusual alterations in haematologic variables were documented by Bowman (2002), who worked on haematologic manifestations in RA. The values equally agreed with results obtained by Peters et al.(1996).Blood films analyses revealed normocytic cells with few microcytic cells. The causes for these alternations could be multifactorial due to disease

activity, drug induced, bone marrow suppression or ineffective erythropoiesis as documented by Harrison (2001) who studied the clinical features of RA. There could equally be premature destruction of red cells which may have caused secondary iron deficiency as was signaled by some microcytic cells observed. This was equally the observation made by Danesi and Taccam (2004).The highly elevated ESR observed could be attributed to response to inflammation caused by the disease. There may be elevation of gamma globulin and fibrinogen as seen in other diseases of chronic disorder. Similar observations were made in male arthritics as recorded in table 4.6. 80% of the subjects had haemoglobin below anaemia , 60% had WBC below normal level, and 25% had low count. No significant statistical differences were observed in lymphocytes and monocytes (P>0.05) as was the case in females. This difference could be suggestive of pathologic differences in disease activity between the two groups or due to genetic differences in the two groups.

Conclusion

This finding is vital to researchers who may want to find out if there are male hormones that could be administered to the females at certain age to stop the development of autoimmune disease without much effect. It is equally interesting to note the adverse the disease had on haematologic variables determined. This is very important findings as it will help in the management of patients and in averting complications which may result from anaemia, leucopenia and thrombocytopenia.

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How to cite this article:

Okoroiwu, I.L, Obeagu, E.I, Obeagu, G.U. Ofor, I.B. (2016). Haematological variables in rheumatoid arthritis patients in Imo state Nigeria . Int. J. Adv. Res. Biol. Sci. 3(4): 91-98.