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A Correlative Study of Alteration of Serum Ferritin, Uric Acid and Magnesium Levels in Autoimmune Diseases Affecting Skin.

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Abstract

Autoimmune diseases are due to abnormal immune response of the body against tissues and cells normally present. It develops when our immune system which defends our body against diseases misinterprets our healthy cells as foreign and eventually starts attacking them. In autoimmune skin diseases the immune system mistakes the skin cell as a pathogen and sends out faulty signal that speeds up the T lymphocyte activation. This study was planned with an objective to determine the levels of serum uric acid, magnesium and ferritin in patients with autoimmune diseases affecting skin and to correlate with the duration and severity of disease. Thirty patients having newly diagnosed autoimmune skin disorders were enrolled in the study. Their serum was subjected to estimation of serum ferritin, uric acid and magnesium. The results were compared with thirty age and sex matched healthy controls. Independent t test was applied for analysing data. The result showed significantly increased levels of uric acid and ferritin ($p<0.05$) in cases as compared to controls. The level of magnesium was not significantly changed. It was concluded that as these disorders are associated with rapid epidermal cell turnover consequently increasing uric acid levels. Serum ferritin is an acute phase reactant and can be identified as a marker of disease severity correlated with duration of disease. Serum levels of uric acid, magnesium may be helpful in understanding the pathophysiology and to develop more effective therapeutic modalities.

Introduction

Autoimmune diseases are due to abnormal immune response of the body against tissues and cells which are normally present. It develops when our immune system which normally defends our body against diseases misinterprets our healthy cells as foreign and eventually starts attacking them. The signs, symptoms and presentation of the disease are a complex phenomenon and depend on various factors like the organs, tissue and area involved. Dermatomyositis, polyarteritis,

scleroderma and other primarily cutaneous disorders have shownmanifestations of autoimmunity,but all of the markers of the autoimmune disease process have not been demonstrated. In autoimmune skin diseases such as dermatomyositis, psoriasis,systemic scleroderma, polyarteritis nodosa, systemic lupus erythematosus (SLE), pemphigus, pyoderma gangrenosum, and eczema, the absence of a specific etiologic agent makes the autoimmune concept more complicating and some similarities between those of the more classic autoimmune diseases, such as rheumatoid arthritis, makes this possibility more feasible.[1,2]

In SLE alterations in the biochemical indices, fibroid degeneration of collagen and intracellular tissues, infiltration of cellular tissues with lymphocytes and plasma cells, diffuse vasculitis, nuclear degradation andresponse to corticosteroid therapy suggest autoimmune disease. Heavier evidence is characterized by nucleophagocytosis by polymorphonuclear neutrophils from peripheral blood and bone marrow induced by different factors in the serum which are γ-globulins representingauto-antibodies directed against the nuclear protein. In autoimmune skin diseases the immune system mistakes the skin cell as a pathogen as it is unable to discriminate between self and non self and sends out faulty signals that speeds up the T lymphocyte activation.[3,4]

Ferritin is nature's unique and conserved approach to controlled, safe use of iron and oxygen, with protein synthesis in animals adjusted by dual, genetic DNA and mRNA sequences that selectively respond to iron or oxidant signals.These sequences ultimately link ferritin to proteins of iron, oxygen and antioxidant metabolism. It is well established that elevated ferritin levels are found in adult Still's disease, but hyperferritinemia has been scantly investigated in other autoimmune diseases.[4,5]

The rationale for evaluating this protein in autoimmune diseases derives from it being an acute phase reactant (APR), and hence increased during inflammation. APRs have been found to be elevated and conducive of activity of disease, such as C-reactive protein (CRP) in rheumatoid arthritis. In SLE, other than an elevated erythrocyte sedimentation rate (ESR), APRs such as serum amyloid component P (SAP), C-reactive protein (CRP), and mannose binding lectin (MBL) are not raised, indicating a possible mechanism of antibody production that blocks their function. To investigate this hypothesis, it has been described that elevated titers of anti-SAP antibodies generally correlatewith disease activity . Studies have shown thataltered states of ferritin function leading to disease and hyperferritinemia reported in various autoimmune diseases.[6]

Uric acid is the final oxidation product of purine metabolism in humans and higher primates. But in most other mammals the enzyme uricase further oxidizes uric acid to allantoin which forms the basis of most of the enzymatic assays used for determination of uric acid in body fluids. Excess serum accumulation of uric acid can lead to a type of arthritis known as gout which may be associated with psoriatic skin disease.[7]

Elevated uric acid, mild anemia, negative nitrogen balance, increased sedimentation rate, increased alpha-macroglobulin, altered lipid profile in the form of high levels of total cholesterol, triglycerides and LDL cholesterol but significantly low HDL cholesterol have been reported in psoriasis. Increased levels of stress hormones like elevated serum cortisol have also been reported in patients with autoimmune disease.[8]

It is known that magnesium is a natural element widely diffused in living organisms, where the largest concentration is found in bones. Magnesium, being a normal component of the blood plasma and a calcium antagonist, takes part in the muscle contraction mechanism and is vital for the action of a number of enzyme catalyzed reactions.. Few studies have shown that at the onset of an autoimmune disease a magnesium depletion takes place throughout the organism due to transfer of the mineral from the bone marrow to the newly formed erythrocyte, and with a massive transfer of the mineral to the areas affected by the autoimmune diseases.[9]

With this background the present study was planned to determine the serumferritin, uric acidand magnesium levels in the patients suffering from autoimmune disease affecting skin and to correlate these parameters with the duration and severity of the disease.

Aim & Objectives

1. To estimate the levels of serum ferritin, uric acid and magnesium in patientssuffering from autoimmune disease affecting skin and to compare with healthy controls.
2. To see the correlation of serum ferritin, uric acid and magnesium levels with duration and severity of the disease

Materials & Methods

The present study was conducted in the Department of Biochemistry in collaboration with the Department of Skin and Venereology, Dermatology Pt. B.D. Sharma PGIMS, Rohtak.In this studythirty patients having newly diagnosed autoimmune skin disorders were enrolled and same number (30) of healthy age and sex matched volunteers served as controls. They were divided in two groups. Group I: Thirty patients (age 18-45 years) having newly diagnosed autoimmune skin disorders as casesGroup II: Thirty age and sex matched healthy controls or comparison were selected.

Inclusion criteria

The new patients provisionally diagnosed by the clinician as suffering from autoimmune skin disorders.

Exclusion criteria

1. Patients having acute illness such as fever, joint pains, abdominal complaints
2. Patients having history suggestive of malignancy
3. Patients on radiotherapy
4. Patients with recent history of chest pain
5. Patients with deep fungal infection
6. Patients having disseminated localized gonococcal infection
7. Patients already taking active systemic therapy

Proper history was taken and thorough clinical examination was performed. All the information was collected on the pretexted structural proforma.

Serum ferritin was measured by chemiluminiscence. The estimation of serum uric acid and magnesium was done on Randox autoanalyzer using standard kits. These results were compared with thirty age and sex matched healthy controls. Independent t test was applied for analyzing data.

Results

The result showed significantly increased levels of uric acid and ferritin in cases as compared to controls. The level of magnesium was not significantly changed although it was found to be on the lower range in the cases. Also the increased levels of uric acid and ferritin were positively correlated with the duration and severity of disease and levels of magnesium showed the negative correlation as lower levels were seen in severely ill patients.

Table I

Parameter	Cases	Controls	p value
Uric Acid (mg/dL)	8.78±0.61	4.85±0.19	<0.05
Magnesium (mg/dL)	1.84±0.31	2.14± 0.26	>0.05
Ferritin (ng/mL)	363.77±9.1	57.76±8.56	<0.001

Fig. 1

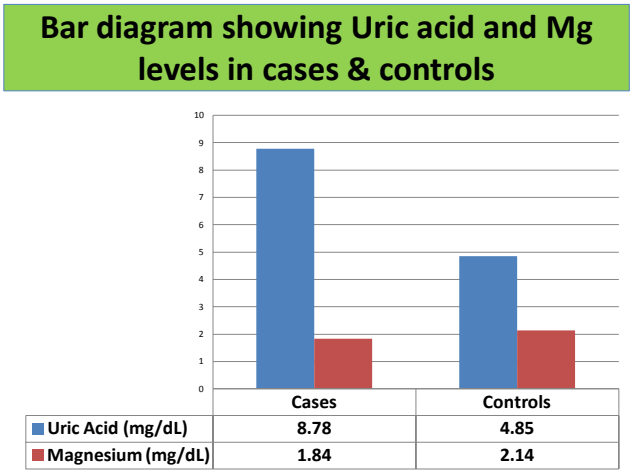
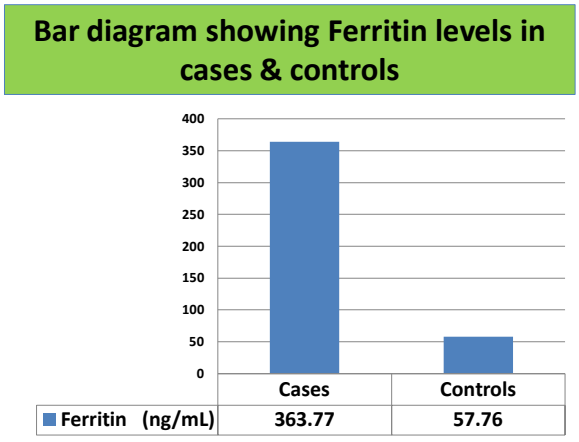


Fig. 2



Discussion

Serum ferritin levels were found to be raised (p value<0.001) significantly compared to controls asthe mean value for serum ferritin level was 363.77±9.1 in cases and 57.76±8.56in the control group. As ferritin is an acute phase reactant the increased levels can be correlated to the duration and severity of disease.Ferritin has been implicated in various diseases and may be important in autoimmune conditions. Hyper-ferritinemia is present in active SLE, RA,and may play a role in cardiac disorders like mitral stenosis Monitoring ferritin levels are important because autoimmune phenomenon is a state where regulatory systems of inflammation are stimulated beyond the physiological limits. There is a state of oxidative stress as the autoimmune disease progresses.[10]

Evidences have shown that macrophage ferritin accumulates during inflammation, when serum iron decreases and iron in specific cells increases. During infection or inflammation, it is the relative iron deficiency created by the host redistribution of iron, with a deficit in serum and an increase in macrophages ferritin synthesized in response to environmental iron deficiency and can be associated with virulence. Ferritin has been reported to exhibit different immunological activities including: binding to T lymphocytes and inhibition of E-rosette formation, decreasing the phagocytosis of granulocytes and regulation of overall immune response. Our findings are consistent with the study done by Zandman-Goddard etal which explains that increased serum ferritin levels are associated with thermogenesis due to lipid peroxidation induced by iron disturbances and altered ferritin function can lead to disease states by mechanisms of inflammation, infection, injury andrepair. Howeverfurther investigation into the mechanisms of ferritin in autoimmune diseases is required.[11]

Uric acid is a strong reducing agent and although an antioxidant hyperuricemia is often associated with arthritis and cardiovascular diseases.But in autoimmune diseases its antioxidant property is overcome by pro-oxidant and pro-inflammatory effects of the accumulation of reactive oxygen species.The mean value for serum uric acid was8.78±0.61in the case

group and4.85±0.19in the control group. From our study it was found to be higher as compared to controls. Alsothere is a significant change in the 'p'value (<0.05).It can be stated that the elevated levels result from accelerated epidermal cell turnover and incomplete differentiation of epidermis as a sequel of the autoimmune attack on the skin cells. The antioxidative effect of uric acid may be prominent in its protection against demyelination in Multiple sclerosis (MS). Several studies reported a significantly higher prevalence of MS (up to 60%) and its components such as hypertension, hyperinsulinemia, hypertriglyceridemia and diabetes in the hyperuricemia population, suggesting that hyperuricemia might be an indicator for early diagnosis of MS and of its different clinical manifestations.[12,13]

However, from a modern medicine point, high uric acid is undesirable. A preponderance of medical literature suggests a link between uric acid elevation and increased cardiovascular disease. Hypertension is also positively associated with high serum uric acid levels. More recently, it has been shown that serum uric acid levels influence the onset of insulin-insensitive diabetes in middle-aged and older people, independently of other established metabolic risk features.[14]It has been reported that high serum uric acid at least at times results in systemic or localized monosodium urate(MSU) crystallization, as crystalline MSU is injurious to many tissues and triggers strong inflammation. The inflammatory effect of MSU crystals is mediated in large part by the increased IL-1β and IL-18 production. IL-1β produced is likely the main agent to trigger systemic inflammation, promoting extensive neutrophil infiltration and tissue restructuring, such as is observed in gout. MSU crystals can be recognized by innate phagocytes, including dendritic cells, macrophages, and neutrophils. It has been shown that antigen-presenting cells (APCs) can sense uric acid as one of the proinflammatory endogenous signals released by damaged cells or tissues. These damage-associated molecular patterns can trigger a systemic inflammatory response similar to pathogen-associated molecular patterns.[15]

Magnesium is now recognized as an important cation.Evidence from epidemiologic studies demonstrated an association between magnesium rich diet and decreased incidence of Diabetes mellitus and its complications. According to other researchers, the condition is due to increased urinary excretion of Mg or dietary deficiency and decreased absorption of magnesium.[16]McNair et al. explained low plasma levels of magnesium , urinary excretion of magnesium and fasting glycemia as being caused by decreased urethral reabsorption of this element in the presence of hyperglycemia. Magnesium supplementation in insulin deficient patients with diabetes improved their insulin sensitivity and decreased atherogenic lipid fractions, while the same supplementation reduced the risk of cardiovascular complications in both types of diabetes [17,18]. In our study the levels were on the lower side and there is significant change in thepvalue. Magnesium is important for many biochemical reactions and low levels may lead to a variety of disturbances affecting body system as thedeficiency can lead to increased production of proinflammatory cytokines, which can have a negative impact on immune response in the form of expression of the symptoms related to immune dysfunction.According to the current medical opinion magnesium is the fuel used by the autoimmune diseases to progress, hence dietary magnesium intake is usually advised in the autoimmune diseases affecting the skin.[19]

Conclusion

Serum levels of ferritin,uric acid and magnesium estimation may be helpful in understanding the pathophysiology and may be monitored during antigen specific immunotherapy.The findings of this study highlights that these biomarkers may play an important role in the prognostic aspect of disease. However, since sample sizes in this study were small, larger numbers need to be studied before definitive conclusions can be drawn. Further biochemical evaluation and optimal approach can be done in this regard.

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