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Serum Prolactin: A diagnostic Marker in Fertile Female Suffering from Rheumatoid Arthritis

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ABSTRACT

Background: RA is more common in females due to sex hormones such as estrogen and prolactin which modulate the immune response. Prolactin is similar to growth hormone and placentary lactogen and is secreted by pituitary lactotrophs having an immune stimulatory effect promoting autoimmunity. Elevated level of prolactin in RA run parallels with fluctuation of disease activity. Prolactin is required for interleukin-2 dependent proliferation of lymphoid cell. Level of estradiol increases with disease severity. Its levels are higher in inflammatory knee exudates of patient with RA.

Study Design: Experimental study

Place and Duration of Study: The study was carried out in the Department of Biochemistry, BMSI, in collaboration of Medical Ward 6, JPMC Karachi (October 2009 to March 2010.

Materials and Methods: 35 diagnosed cases of RA were selected with their consent. From general population, thirty five normal healthy subjects were selected for comparison. In the present study the serum levels of prolactin, estrogen, ESR, and RA factor were determined.

Results: The results of our study showed that in patients suffering from RA showed highly significant results ($p<0.001$) of prolactin, estrogen, ESR and RA factor.

Conclusion: Increased serum status of prolactin and estrogen in patients with rheumatoid arthritis (RA), may serve as marker for diagnosis, and prognosis.

Key Words: Rheumatoid Arthritis. Prolactin, Autoimmune Diseases, Estrogen

INTRODUCTION

Rheumatoid arthritis is an autoimmune disease that causes chronic inflammation of the joints and tissue around it. Elevated level of prolactin, estrogen, aldosterone and progesterone in inflamed knee exudates in rheumatoid arthritis suggest that these hormones are present in synovial fluid, may affect the local inflammatory process. The female disposition to this condition may be attributed to the influence of estrogen and prolactin on the bone response[1]. Patient with autoimmune diseases leads to higher production of IgG and IgM in blood and IL-6 in synovial fibroblast. Estradiol seems to exert a proinflammatory effect[2]. In this disease auto antibodies are formed against IgG. These auto antibodies are called rheumatoid factor and are of the IgM class.

RA affects primarily women between the ages of 30 and 50 years. A person with HLA-DR4 genes are predisposed to RA, the agents that induces these auto antibodies is unknown. Evidence has supported the hypothesis that elevation of serum prolactin participates in pathogenesis of autoimmune disease[3].

Although prolactin was initially regarded as an exclusive pituitary hormone, but latter on it was found that non pituitary tissues also produce this hormone. The most important extra pituitary sites that produce prolactin are the deciduas, brain, endometrium and the immune system [4].

MATERIALS AND METHODS

A total of 70 subjects were included in this study. A structured questionnaire regarding the demographic data was filled in by each patient. Consent was also obtained from the patient as well as control subjects. The subjects were divided into two groups: Group A, comprised of 35 diagnosed cases of Rheumatoid arthritis in fertile female patient age ranges between 16 to 45years.

Group B, comprised of 35 age matched healthy control group of fertile female from the general population having normal serum prolactin level.

According to American college of Rheumatology the selection criteria for RA is [5] the patient fulfilling at least four of the following criteria's for rheumatoid arthritis.

1). Morning stiffness in and around joints. 2). Soft tissues swelling of three or more joints. 3). Small joints of both the hands and wrist are involved 4). Rheumatoid nodules 5). Lab findings like rheumatoid factor 6). Radiographic changes.

Inclusion Criteria: Diagnosed cases of RA in fertile female.

Exclusion Criteria: Patients with diabetes mellitus. Infertility

Age below 16 and above 45.
Patient taking steroids.
Patient taking oral contraceptive.
Lactating mothers.
Any thyroid disease.
Pregnancy.

Sample Collection and Storage: Intravenous fasting blood 6 to 8 ml was collected from each patient and control subject. 2 ml blood was transferred to ESR tube containing ethylene diaminetetraacetic acid (EDTA) as anticoagulant. The remaining was transferred to a centrifuge tube and then centrifuged for 10 minutes. Serum of RA patients and control group were analyzed for biochemical parameters. Serum prolactin, serum estrogen and were estimated by ELISA method, rheumatoid factor was estimated by latex agglutination test, ESR was done by Western gren method.

RESULTS

In table 1, comparison of biophysical variable in rheumatoid arthritis and aged matched control group were observed, which showed statistically insignificant difference in age, menarche, parity and BMI as compared to control subject, by using student t-test.

Table 2, shows the comparison of mean values (± SEM) of biochemical parameter in rheumatoid arthritis and control subjects. Serum prolactin, estrogen, rheumatoid factor and ESR were found significantly high with $p<0.001$ when compared with normal subject by using student t-test.

Table 3 shows percentage distribution of patient among rheumatoid arthritis with respect to age and disease severity. A total of 10 cases were seen with rheumatoid arthritis in younger age group i.e. below 25 years , out of which 7(70%) showed disease severity. In the age group above 25 years 23(92%) showed disease severity in rheumatoid arthritis, it shows significant association with $p< 0.01$ when Pearson chi square test applied.

Table No.1: Comparison of Biophysical Parameters Between Rheumatoid Arthritis (RR) with Control Groups (Values are expressed as Mean ± SEM)

Parameters	Control (n=35)	RA (n=35)
Age (Years)	28.71 ±1.13	31.15 ±0.98
Menarche (Years)	12.63 ±0.17	12.74 ±0.18
Parity	2.46 ±0.27	2.83 ±0.29
BMI (Kg/m^2)	21.78 ±0.66	21.79 ±0.55

*Significant difference with P<0.001.When compared with control.

Table No.2: Comparison of Hormones, RA Factor and ESR between Rheumatoid Arthritis (RA) with Control Groups. (Values are expressed as Mean ± SEM)

Parameters	Control (n=35)	RA (n=35)
Serum prolactin (ng.ml)	9.92 ±0.70	34.65* ±1.01
Serum estrogen (Pg/ml)	30.31 ±4.79	84.58* ±1.57
RA factor (IU/ml)	16.47 ±0.62	131.82* ±7.26
ESR (mm/hr)	17.70 ±0.86	88.19* ±2.06

* Significant difference with P<0.001. When compared with control.

Table No.3: Percentage Distribution of Patients among RA Group with Respect to Age and Disease Severity (Percentages in parenthesis)

Age	RA Group	
(Years)	Total no of Patients	Severity of Disease obtained (Prolactin >35ng/ml)
16-25	10	7 (70%)*
26-45	25	23 (92%)*

*Significant association with p<0.01 by Pearson chi-square test.

DISCUSSION

Prolactin has the potential to play a role in pathogenesis of autoimmune diseases. The immune system is directly influenced through thymus. Thymic epithelial cells have high expression of prolactin receptor. Prolactin enhances release of thymocytes from thymus which is carried out by surface adhesion molecules[6].

Rheumatoid arthritis is a condition that causes pain, swelling, and inflammation in joints. Initially the joints of the hands and feet are affected but in later stages other joints can be affected. RA can make joints feel stiff and can leave a feeling of tiredness and unwell. RA is an autoimmune disease where immune system, which usually fights against infection, attacks the lining of joints causing them to become inflamed by the passage of time joints may become permanently damaged. The symptoms of rheumatoid arthritis usually come and go, sometime it shows mild discomfort and sometime it can be very painful making it difficult to do everyday tasks this worse condition is called flare up making rheumatoid arthritis difficult to live with[7].

The regulation of inflammatory process is tightly controlled by involving both mediators that initiate and maintained inflammation and those which shut the process down. In state of chronic inflammation an imbalance between two mediators leave inflammation unchecked resulting in cellular damaged. In case of rheumatoid arthritis this is manifested by destruction of

cartilage and bones[8]. The long term prognosis is poor 80% of effected patient are disabled after 20 years and life expectancy is reduced by an average of 3-18 years prevalence of the disease is 0.5 % to 1%[9]. Rheumatoid arthritis can affect anyone at any age, but it usually develops between the ages of 30 and 50. More than 75% of those affected are women[10].

In the present study, the incidence of disease severity in rheumatoid arthritis was found in the later age (above 25 years) in the local population this is favored by one of the study [11], in which the functional capacity was markedly decreased in the older patients. Onset of the disease is usually in middle age, but it can occur in some individual as early as 20 years.

There is an increase prevalence of low body mass in RA in female group but in acute phase it was inverse relation[12]. BMI is used as one of the bio-physical parameter and was found non-significant in other studies as well as in our study. Various studies shows that low BMI improve disease prognosis but in RA it is seen that when patient loose weight then chances of more risk of disability happened[13]. It was seen in one of the study that low BMI at the beginning of RA could increase disease severity[14].

Parity in RA patient which was found statistically non-significant

In present study we observed significantly high levels of serum prolactin in RA patients, these finding are in consistent with other studies [15]. Another study also indicates the higher serum prolactin levels in patient with rheumatoid arthritis. It was [16]suggested that prolactin may have pathogenic role in RA, studies have shown that prolactin enhances inflammatory response and increase prolactin concentration have been reported in patient with RA.

A study described that sex hormone appears to play an important role as modulator of autoimmune disease on set, estrogen enhances humorol immunity, serum level of estrogen has been significantly elevated in RA patient particularly synovial fluid level when compared with control, and these findings are in agreement with our study where we observed significantly increased level of estrogen[2]. But[17] Latmen it was indicated that estrogen exhibit anti-inflammatory and anti-arthritic activity and women with RA, might be expected to have reduction to have some symptom of RA our result have high estrogen level in RA is in disagreement with said study.

Rheumatoid Factor is an antibody that is measurable in the blood. RA factor is actually an antibody that can bind to other antibodies. Antibodies are normal protein which normally present in our blood and are important part of our immune system. RA factor is an antibody that is not usually present in normal individual, 80% of rheumatoid arthritis patient have positive RA factor. Our study show significantly high value of RA factor in RA and is totally in agreement with the other studies[18].

Erythrocyte sedimentation rate (ESR) is useful as a screening test to identify patient with inflammatory conditions. The western gren method is the procedure of choice to measure ESR. It is a useful marker to monitor disease activity of RA. Our Data suggest that ESR is elevated in RA and can be used to asses disease activity in a very inexpensive way. Other researchers[19] also suggest that ESR can be used as diagnostic tool.

Prolactin showed strong correlation with disease severity, which is in agreement with other researches[18], it was found consistent with one of the study[20] who expressed that prolactin correlated negatively in patient with rheumatoid arthritis.

CONCLUSION

Increased serum status of prolactin and estrogen in patients with rheumatoid arthritis (RA), may serve as marker for diagnosis, and prognosis.

Suggestions: We recommend that serum prolactin must be analyzed for monitoring the disease as well as for diagnosing the disease, and can be used therapeutically (treatment with anti-prolactin drugs) to prevent deformities.

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