Evaluation of Serum Prolactin as a Marker of Inflammation in Spondyloarthritis

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ABSTRACT

Introduction: Colour vision defect (CVD) is the inability to perceive colour differences under normal lighting conditions. Its prevalence thought to be around 7% for men and 0.4% for women, vary from country to country, between regions in the same country, as well as between ethnic groups. Its importance lies in the fact that it is prevents a person from doing certain jobs while creating difficulties in others. Screening for CVD during childhood and counseling to guide them towards choosing appropriate career needs to be carried out.

Material and methods: Records of pre employment screening from the period 1st January 2016 to 30th April 2020 preserved in the Department of Medical Examination-I, of Atal Bihari Vajpayee Institute of Medical Sciences and associated Dr Ram Manohar Lohia Hospital were examined for the purpose of the study. The number of candidates having CVD was tabulated. Colour vision testing had been done using Ishihara's plates.

Results: A total of 13179 candidates were screened during the period out of which 9879 were males (75%) and 3300 females (25%). 384 males (3.89%, 95% CI: 3.51%, 4.27%) and only 6 females (0.18%, 95% CI: 0.17%, 0.19%) were found to be colour vision defective giving a overall prevalence of 2.98%. There was an increase in the prevalence of colour vision defect after age 50.

Conclusions: Prevalence of colour vision defects in males is 3.89% (95%CI 3.51, 4.27%) and that of females is 0.18% (95% CI 0.17, 0.19). Screening for CVD at an early age will be beneficial to children in helping them to choose their career in light of their deficiency.

Keywords: Colour Vision Deficiency, Protanopia, Deuteranopia, Triatanopia, Gene therapy, pre- employment screening.

MeSH Terms: Achromatopsia, Color Blindness, Color Vision Deficiency

INTRODUCTION

Spondyloarthropathies (SpA) are a group of chronic multisystem inflammatory disorders and includes Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), and Reactive Arthritis (ReA) among others. Long-term outcomes of SpA are permanent physical and functional damage as well as lifelong disability if left undiagnosed and untreated[1]. Monitoring of the disease activity is critical to initiate or change therapy and uses various scores like BASDAI, and ASDAS.

Conventionally used measures of Disease activity such as BASDAI and ASDAS, are subjective in nature. They are therefore dependent upon the patient's perception of his/her symptoms[2]. CRP and ESR, the most commonly used markers of systemic inflammation are found to have low sensitivity and specificity[3] besides being affected by factors that are not related to inflammation[4]. Thus they are not adequate to assess disease activity in all patients. Research is presently focussed to find out more promising biomarkers for assessment of disease activity in SpA[5].

Prolactin, a hormone synthesized and released by the anterior pituitary gland has been found to have immunomodulatory action along with other hormonal and metabolic roles. It has been found to correlate with disease activity in patients of SLE[6], RA[7], and recently in PsA[8]. This study aims to evaluate if serum Prolactin levels can be used as an objective parameter for assessing inflammation and disease activity in spondyloarthritis vis-a-vis CRP levels.

MATERIAL AND METHODS

Forty eight adult patients fulfilling the ASAS criteria for Spondyloarthritis[9] were included in the study after application of the exclusion criteria. Thirty two age and gender matched controls were taken. Exclusion criteria included patients having serum creatinine more than 1.5mg/dl, hepatic serum transaminase levels more than three times the upper normal limit, hypothyroidism, concurrent lymphoproliferative or malignant disease or infection, severe persistent headache or any symptom suggestive of an intracranial pathology, known or diagnosed case of epilepsy, or depressive illness, diabetes, hypertension, patients taking protein pump inhibitors, H2 blockers, antipsychotics, anti-epileptics, and anti-emetics, pregnant ladies, nursing mothers or those who have breastfed in last the 2 years, and patients of SpA having overlap with other connective tissue disorders. Disease activity was assessed by using ASDAS-CRP and BASDAI. Relevant clinical and laboratory parameters were recorded. For measurement of serum Prolactin, three samples were collected in early morning with patient in fasting state and at least 1 hour after waking up and after 30 minutes of rest, and a gap of 15 minutes between two successive samples, to account for the fluctuating levels of Prolactin. Equal amount

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Parameter	Cases	Controls	P value
Age (years)	33.5 (26 – 39.5)	28 (26 - 32)	0.06
Gender	Male : 42 Female : 6	Male : 26 Female : 6	0.44
CRP (mg/dL)	1.49 ± 1.68	0.54 ± 0.11	<0.001
Serum Prolactin (ng/mL)	10.15 ± 5.98	10.32 ± 3.33	0.126

Table-1: Table showing comparison between cases and controls.

Disease activity Variable	Moderate (N=5)	High (N=33)	Very high (N=10)	P value
CRP (mg/dL)	0.52 ± 0.04	0.92 ± 0.6	3.88 ± 2.33	< 0.001
Prolactin (ng/mL)	6.08 ± 1.72	11.04 ± 6.68	9.26 ± 3.78	0.067

Table-2: Table showing values of CRP, and Prolactin between different disease activity groups based on ASDAS-CRP

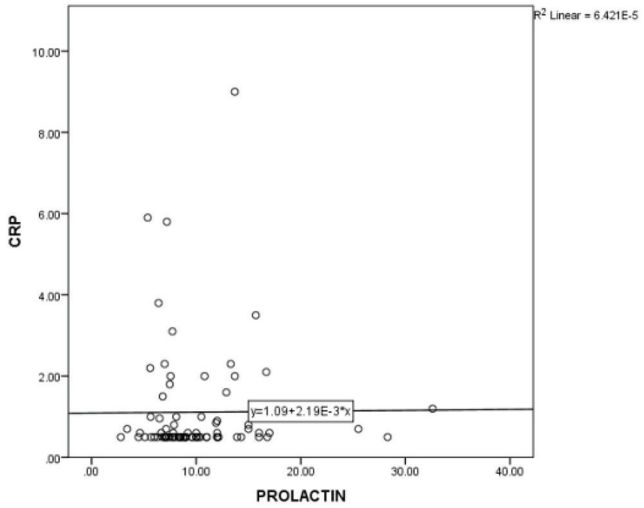

Figure-1: scatter diagram showing correlation between Prolactin and CRP

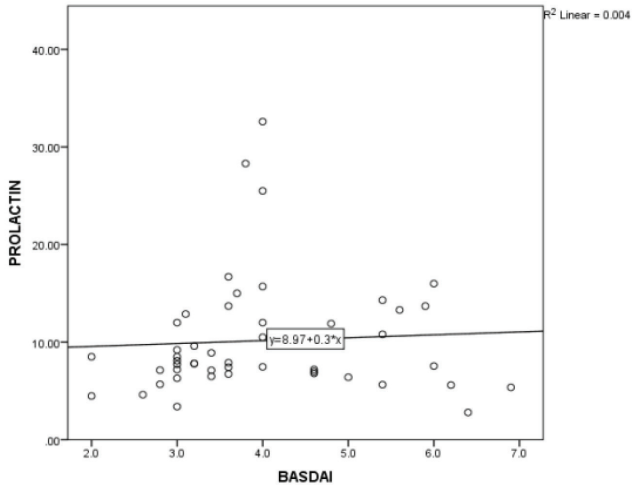

Figure-2: Scatter diagram showing correlation between BASDAI and Prolactin

of serum from each sample was mixed together and the pooled serum was used for the estimation of serum Prolactin levels.

The data was entered in a Microsoft Excel spread sheet and analysis was done using Epi-Info, and JASP statistical packages. Continuous variables are represented as Mean ± Standard Deviation (SD) or Medians with Inter-quartile range (IQR). Categorical variables are represented as number and percentage (%). The variables were tested for normality with the Kolmogorov-Smirnov test, Q-Q plots, visual inspection of the histograms and the z-scores for the degree of skewness and kurtosis. All tests of significance were two-tailed and statistical significance was defined as $P < 0.05$. Correlation coefficient was used to find out the strength of correlation between two variables. Since all variables did not meet the assumptions required for parametric tests, hence non-parametric tests (i.e., Mann-Whitney test, Spearman correlation) were used for all analyses for consistency.

RESULTS AND OBSERVATIONS

The cases and controls were matched with respect to age and gender and there was no significant difference between them. 40 of the 48 cases (83.3%) were HLA B27 positive. Disease activity of the cases by ASDAS-CRP was 2.85 ± 0.76 with median of 2.7 (2.2 – 3.3) and IQR (25-75) of 1.8 to 5. The parameters are summarised in Table 1.

The cases were further subdivided into four groups namely Inactive, Moderate Activity, High Activity and Very High Activity based on disease activity as per ASDAS-CRP[10]. Since our cohort contained no cases in remission, there were only three groups. Prolactin, CRP levels were compared between the groups. The results are tabulated in Table 2.

Prolactin levels did not differ significantly between the different disease activity groups. There was no significant correlation between Prolactin levels and CRP (p=0.583) [Fig 1] or ASDAS-CRP (p=0.417) or BASDAI (p=0.299) [Fig 2].

DISCUSSION

In order to be classified as a "Marker of Inflammation", a parameter should meet at least 3 criteria[3].

Discrimination: The ability to discriminate between those who have a disease and those who do not.

Proportionality: The parameter should rise (or fall) progressively with increasing disease activity.

Operational feasibility: The time, cost, availability and ease of measurement should be such that it is feasible to measure the marker in a large enough group of people.

It should also demonstrate superiority or a non inferiority to the existing gold standard marker of inflammation, which presently is CRP[11]. CRP undoubtedly fulfils these conditions and is thus a part of the ASAS classification criteria as well as the ASDAS scoring system. Prolactin to be effective as an inflammatory marker in spondyloarthritis should also fulfil these conditions too. It should also correlate with already validated scores used in Spondyloarthritis like BASDAI and ASDAS.

In our study, Prolactin did not differ significantly between diseases and controls. Rather, the levels in controls were marginally higher. This may possibly be caused by the anxiety and stress of visiting hospital for over an hour for collection of samples, as stress is known to alter the levels of Prolactin [12,13].

When our cases were subdivided into groups based on disease activity states as measured by ASDAS-CRP, the levels were found to be higher in high disease activity and lower in the very high disease activity groups, which is contrary to what is expected from an inflammatory marker. Prolactin levels also did not show any correlation with BASDAI, or ASDAS. One of the reasons may be the small sample size and a larger sample may have yielded different results. This is one limitation of our study along with the other limitation of controls being less in number than cases. However, it is to be noted that this study took place during the time of the covid19 pandemic and it would have been unethical to call patients as well as healthy volunteers to visit the hospital.

Prolactin has a circadian rhythm, and is easily affected by stress and over the counter medications like proton pump inhibitor-domperidone combination[14] which are very commonly used in our country. Besides, it needs early morning pooled samples which is not easily available especially in resource constrained settings, and is more expensive than ESR and CRP. Thus it fails the operational feasibility aspects required for a test compared to CRP.

Thus we conclude that serum Prolactin may have a more important role in diseases like SLE and RA which are common in females, but cannot at present replace CRP as a marker of inflammation in cases of spondyloarthritis.

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