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EVALUATING SERUM D-DIMER LEVELS AS A BIOMARKER FOR SEVERITY AND PROGNOSIS IN CHRONIC URTICARIA.

Biochemistry

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ABSTRACT

Background: Chronic urticaria is characterized by transient swellings of the skin, which can be extremely disabling and difficult- to-treat. The burden of the disease is on the increase and challenge still remains to identify newer biomarkers for indicating disease severity and disease control. The study was planned to investigate the usefulness of D-dimer estimation in patients of chronic urticaria as an indicator of disease prognosis and severity. **Methods:** 100 diagnosed patients of chronic urticaria formed the study group. Patients with any systemic disease that could alter the coagulation cascade or patients on anti-coagulant therapy were excluded from the study. D-dimer levels were estimated at the time of enrolment by spectrophotometric analysis and levels more than 0.5 µg FEU/ml were taken as elevated. Disease severity was assessed by the EAACI/GA2LEN/EDF activity score and based on the score subjects were grouped into mild, moderate and severe groups. D-dimer levels and disease activity score were analyzed again after 2 months of treatment with antihistaminic. Data was expressed as mean ± SD and students t test was used for comparison of parameters. Correlation between D Dimer levels and disease activity score was calculated using pearson's correlation coefficient. **Results:** The mean disease activity score of the subjects at the time of enrolment and 2 months follow up was 3.97 ± 1.2 and 2.76±1.13, respectively. The mean disease activity score was found to be significantly different between the three subgroups with $p<0.0001$. The disease activity score in patients with moderate and severe chronic urticaria decreased significantly after treatment. ($p<0.0001$).The mean D Dimer levels decreased significantly after treatment (from 1.02±1.10 µg FEU/ml to 0.54 ± 0.75µg FEU/ml, $p<0.001$). A statistically significant positive correlation was found between levels of D Dimer and the disease activity score. ($r=0.71$, $p<0.0001$). **Conclusions :** The results of the study showed that the patients of chronic urticaria had elevated levels of D Dimer, which showed an increasing trend with increase in the severity of the disease. D Dimer measurement is easily available and thus represents a potentially ideal candidate prognostic marker for chronic urticaria.

KEYWORDS

Chronic urticaria, D Dimer, Disease activity score

INTRODUCTION

Chronic urticaria is a fairly common condition, with prevalence in adults varying from 20 to 30%. [1] Chronic urticaria (CU) is characterized by recurrent eruption of itchy short-lived wheals and flares for longer than six weeks duration. It can be an extremely disabling and difficult-to-treat condition. Chronic urticaria has multifactorial aetiologies including intolerance to food or drugs, infectious diseases, allergens and autoimmune processes.

Urticaria is caused by degranulation of cutaneous mast cells which release potent vasoactive mediators that induce vasodilatation and increased capillary permeability, resulting in erythema and wheal formation. Itching and pain are caused by sensory nerve stimulation. The main vasoactive mediator is histamine. The pathogenesis of CU includes immunological and non-immunological types and an idiopathic type which includes those patients in which no identifiable causes can be detected after full investigation. The immunological type is associated with the presence of histamine-releasing IgG autoantibodies. Recent reports have revealed that patients with CU show signs of thrombin generation and activation of the tissue factor pathway of the coagulation cascade. D dimer is a fibrin degradation product formed during the lysis of a thrombus. D-dimer elevations are detected during increased fibrinolytic activity. Some reports have associated levels of D dimer with chronic urticaria. However, there is insufficient data available about this association from this part of the world.

The burden of the disease is on the increase and challenge still remains to identify newer biomarkers for indicating disease severity and disease control. If the association between D-dimer levels and severity of chronic urticaria can be established, it can be used to aid treatment protocols and help decrease the morbidity in patients with chronic urticaria.

The study was thus planned to investigate the usefulness of D-dimer estimation in patients of chronic Urticaria as an indicator of disease severity and disease control.

MATERIALS & METHODS

The prospective study was conducted in the Department of Biochemistry & Dermatology, Government Medical College & Hospital, Chandigarh. The study was approved by the Institutional Research and Ethics committee. The study received financial grant from DST Chandigarh.

The study group included 100 patients more than 18 years of age diagnosed with chronic urticaria with duration of disease more than 6 months. The sample size was calculated with a disease prevalence of 15-20% in the Indian population.[1] (at 95% confidence level & 10% CI, with 20 % prevalence of chronic urticaria in the population of Chandigarh).Patients with any other systemic disease that could alter the coagulation cascade or patients on Anti-coagulant therapy were excluded.

Detailed history and informed written consent was obtained from patient/ next of kin. In addition to the required investigations, 5 ml of venous blood sample was taken under all aseptic conditions for estimation of D-dimer levels by spectrophotometric test on Modular P800 Random Access Chemistry Analyzer, at the time of enrollment.[9] D Dimer levels more than 0.5 µg FEU/ml were taken as elevated. Disease severity was assessed by the EAACI/GA2LEN/EDF activity score.[10]

The disease activity was scored from 0-6 and patients with score 1-2 were graded as mild, 3-4 as moderate and 5-6 as severe disease activity. The subjects of the study group were regrouped into three sub-groups (mild, moderate and severe) on the basis of the disease activity score. The subjects were given regular treatment with antihistaminics (Tab Cetrizine 10 mg once a day).

This was a prospective study and patients were analyzed for levels of D-dimer, again after 2 monthof treatment with antihistaminics (Tab Cetrizine 10 mg once a day). Subjects were followed up after 2 months and D Dimer levels and Diseases activity score was reassessed.

Statistical analysis was done to ascertain the relationship between

levels of D-dimer and disease severity and disease control, in patients of chronic Urticaria.

Statistical Analysis

Data was expressed as mean ± SD .Comparison of parameters between the groups was done by student's unpaired 't' test and within groups by paired 't' test with level of statistical significance set as p<0.05. The correlation between D Dimer levels and disease activity score was calculated using pearson's correlation coefficient.

RESULTS

The study group consisted of 100 patients diagnosed with chronic urticaria. The mean disease activity score of the subjects of the study group at the time of enrolment was 3.97 ± 1.2. The mean score was found to decrease at two months follow up after treatment and levels were 2.76±1.13. This decrease was found to be statistically significant (p<0.0001)

The subjects of the study group were sub-grouped at the time of enrolment into mild, moderate and severe on the basis of the disease activity score. The mean scores of each subgroup are shown in Table 1.

Table 1 : Disease activity score and D Dimer levels in the subjects of the study group.

	Mild	Moderate	Severe
Disease activity score	1-2	3-4	5-6
Percentage of subjects	14%	63%	23%
Initial disease activity score (Mean ± SD)	2 ±0	3.75±0.43	5.71±0.46
Disease activity score after treatment (Mean ± SD)	2.1±0.71	2.44±0.95	3.95±0.97
D Dimer Initial levels µg FEU/ml (Mean ± SD)	0.42 ± 0.31	0.60±0.39	2.51±0.64
D Dimer levels after treatment µg FEU/ml (Mean ± SD)	0.32±0.53	0.39±0.14	1.07±0.64

The mean disease activity score was found to be significantly different between the three subgroups with p<0.0001. The disease activity score in patients with moderate and severe chronic urticaria was found to decrease significantly after treatment. (p<0.0001) (Fig 1). The scores in patients with mild form of the disease however, did not show any significant change.

The mean D Dimer levels in the subjects of the study at the time of enrolment were higher than normal levels (1.02±1.10 µg FEU/ml). The levels were found to significantly decrease after treatment (p<0.001). The levels of D Dimer showed an increasing trend with increase in severity of chronic urticaria. The levels were found to be different in the three subgroups, with the lowest being in the mild form and the highest in severe form of the disease. (Fig 2)

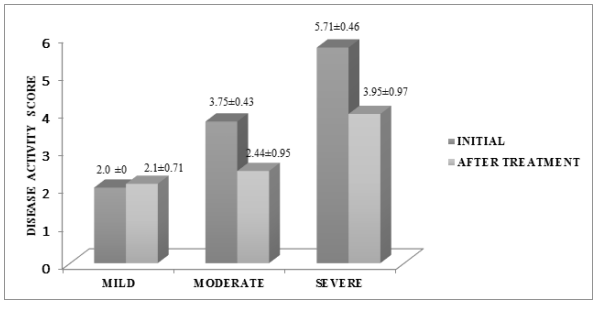

Fig 1: Mean Disease Activity Score In Patients Of Study Group: Before And After Treatment

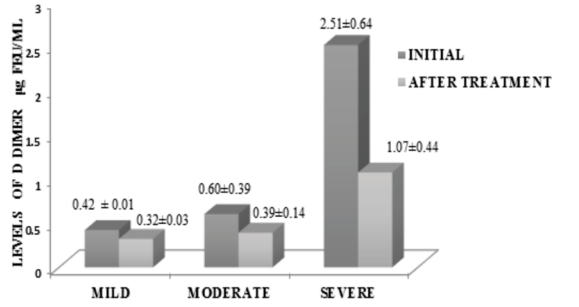

Fig 2 : Levels Of D Dimer In Patients Of Study Group: Before And After Treatment

An association of disease severity with the activation of coagulation cascade was observed in the patients of the study group. Patients of chronic urticaria with severe form of the disease showed higher plasma levels of D Dimer as compared to those with the milder form of the disease. A statistically significant positive correlation was found between levels of D Dimer and the disease activity score. (r=0.71, p<0.0001)

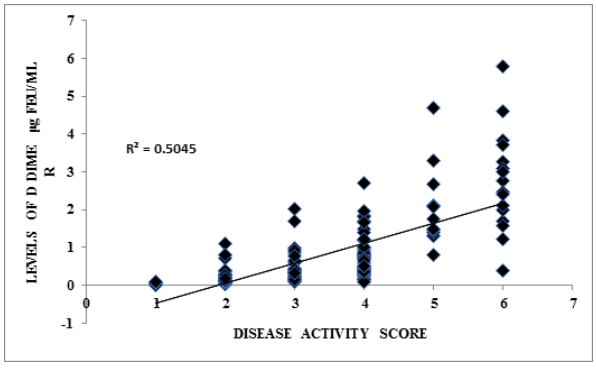

Fig 3: Correlation Between Levels Of D Dimer And Disease Activity Score In Patients Of The Study Group

DISCUSSION

Chronic urticaria has a wide spectrum of clinical presentations and etiologies.[2] Urticaria is caused by degranulation of mast cells and release of vasoactive mediators which in turn cause vasodilatation and increased capillary permeability, resulting in the erythema and wheal formation which is the hallmark of the disease. Autoimmunity is mainly involved in the pathogenesis of chronic urticaria, as proven by the detection of auto-antibodies.[3] However, recent research has suggested that besides autoimmunity other causes of chronic urticaria can also be speculated upon.

In a study conducted by Fagiolo etal, it was found that IgG depleted serum from chronic urticaria patients retained the ability to induce a wheal and flare reaction, suggesting that other mechanisms may also be involved in pathogenesis of chronic urticaria.[4] In another study it was found that the percentage of positive autologous plasma skin testing (APST) is higher than that of positive autologous serum skin testing (ASST) by 80% to 50% respectively.[5] This difference suggested that the coagulation cascade may be involved in the pathogenesis of chronic urticaria. Asero et al in his study found elevated levels of plasma prothrombin fragment in patients of chronic Urticaria.[6] Thrombin is involved in hemostasis including vessel wall wound healing. It increases vascular permeability, stimulates mast cells degranulation and may activate protease activated receptor 1 (PAR 1) on mast cells, which may be the pathophysiology behind chronic Urticaria.[3] Takeda etal, also found a hypercoagulable pattern in patients with chronic urticaria.[7] Some studies have demonstrated higher levels of D Dimer in patients with chronic urticaria.[6,8]

The results of the present study are similar to those obtained by the earlier studies of increased D Dimer levels in patients with chronic urticaria. Further, the results of this study show an increasing trend in levels of D Dimer with increase in severity of the disease. The levels of D Dimer were also found to significantly decrease after treatment and also showed a significant positive correlation with the disease activity score.

The results again emphasize the role of coagulation cascade in the pathogenesis of chronic urticaria. The activation of coagulation cascade may be due to the involvement of eosinophils and a tissue factor pathway, with generation of thrombin potentially contributing to an increased vascular permeability. The results suggest the utility of plasma levels of D Dimer not only in categorizing the severity of the disease but also as a prognostic indicator in reflecting the patient's response to treatment.

CONCLUSION

In conclusion, this study demonstrates a clear association between elevated D-dimer levels and the severity of chronic urticaria,

suggesting that D-dimer could serve as a valuable prognostic marker for this condition. Given its accessibility and ease of measurement, D-dimer offers a practical tool for clinicians in assessing disease progression and potentially guiding treatment decisions. Future research should explore the underlying mechanisms linking D-dimer elevation to chronic urticaria severity and evaluate the utility of D-dimer in larger, more diverse patient populations. This could solidify its role in clinical practice and improve the management of chronic urticaria.

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