Correlation of mean platelet volume levels with severity of chronic urticaria

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Abstract

Background: Chronic urticaria (CU) is a multifactorial disease, however, in a majority of patients, it is not possible to ascribe a specific aetiology, which is termed ‘idiopathic’. Although autoimmunity has been implicated as a principal cause in 30–50% of these idiopathic cases, activation of coagulatory and inflammatory cascades has gained attention in last few years.

Aims: To evaluate levels of mean platelet volume, an indicator of platelet activity, in patients with chronic urticaria and determine its correlation with its severity.

Methods: Mean platelet volume levels were assessed in 194 patients with chronic urticaria and were compared with equal number of age and sex matched controls. Its levels were also correlated with the severity of urticaria and results of autologous serum skin test.

Result: Mean platelet volume (MPV) levels were found to be higher in patients with ASST positive chronic urticaria compared to patients with ASST negative chronic urticaria and controls. MPV levels also showed a positive correlation with the severity of chronic urticaria.

Conclusion: As platelets secrete and express a number of crucial mediators of coagulation and inflammation, coagulation and inflammatory cascades may play a positive role in chronic urticaria, paving the way for better understanding of pathogenesis and introduction of newer drugs.

Keywords: Autologous serum skin test; Chronic urticaria; Mean platelet volume

1. Introduction

The term urticaria is used to denote a disease characterised by short-lived itchy weals, angio-oedema or both together (Gratton CEH and Humphreys F on behalf of the British Association of Dermatologists Therapy Guidelines and Audit Subcommittee, 2007). When urticaria is present daily or almost daily for more than 6 weeks, it is called chronic (Gratton and Kobza Black, 2010).

The causative factor is difficult to identify in chronic urticaria. When there is no detectable cause, it is known as chronic idiopathic urticaria (Champion et al., 1969). Autoimmunity has been implicated as a principal cause of chronic urticaria, potentially explaining 30–50% of previously idiopathic cases (Asero et al., 2001). A number of other factors have been implicated including drugs (Gratton, 2003), foods and food additives (Atkins, 1991), contactants (Williams et al., 2008), infections (Masood and Imran, 2008; Tebbe et al., 1996; Varda et al., 1983; Kanazawa et al., 1998; Serrano, 1975), infestations by intestinal parasites (Chirila
et al., 1981; Walfrom et al., 1995), physical stimuli (Illig, 1973; Kobza Black, 1985; Champion, 1988) psychological factors (Koblenzer, 1983) and other autoimmune diseases. A highly significant linkage of HLA DRB1*04 (DR4) and its associated allele DQB1*0303 (DR8) with histamine releasing autoantibody has also been found in chronic urticaria (O’Donnel et al., 1999).

Urticaria occurs due to a local increase in permeability of capillaries and venules. These changes are dependent on activation of cutaneous mast cells in nearly all types of urticaria (Grattan et al., 1997). In autoimmune chronic urticaria, the participation of various pathogenic autoantibodies, has been postulated, targetting epitopes on IgE protein itself or α-chain of its high affinity FcεRI receptor, ultimately causing the release of histamine from mast cells (Fiebiger et al., 1995). Autologous serum skin test (ASST) is the only practicable test available to the clinicians to detect autoimmune urticaria. Confirmation is needed by in vitro testing for anti-IgE or FcεRIα autoantibodies (Greaves, 2000).

Recent studies demonstrated that activation of a coagulation cascade resulting in thrombin production (Asero et al., 2007) is a prominent feature of exacerbation of chronic urticaria. Within the coagulation cascade thrombin is a serine protease that induces activation of platelets and may play a key role in chronic urticaria (Lundbland and White, 2005).

Platelets secrete and express a large number of substances that are crucial mediators of coagulation, inflammation, thrombosis and atherosclerosis. Mean platelet volume (MPV) is the most commonly used measure of platelet size and is a potential marker of platelet reactivity (Coppinger et al., 2004; Gawaz et al., 2005). Studies indicate platelet volume is in direct correlation with platelet function because large platelets are more reactive. Large platelets are denser, and produce more thromboxane B2 per unit volume of platelet cytoplasm (Martin et al., 1983). Several studies report a correlation between high MPV values and increased disease activity and inflammatory markers (Milovanovic et al., 2004; Canpolat et al., 2010; Yazici et al., 2010; Purnak et al., 2011).

2. Materials and methods

This study was a prospective, hospital based, case controlled study conducted on 194 patients of chronic urticaria attending the outpatient block of the postgraduate department of Dermatology, in our hospital.

An informed consent, basic demographic information and complete history were taken from each patient.

Clinical evaluation of the severity of chronic urticaria was done in each patient. Severity of chronic urticaria was calculated from the sum of individual scores (Bajaj et al., 2008) (Table 1).

An equal number of age and sex matched controls, attending the Dermatology OPD for insignificant complaints unrelated to chronic urticaria was taken. Chronic medical disorders such as diabetes mellitus, hypertension, autoimmune diseases, liver diseases, malignancies and intake of medication for the last 3 months were excluded in history.

All cases and controls underwent a general physical examination, systemic examination, mucocutaneous examination and complete blood count with mean platelet volume in femtolitres (fl) using an automated blood counter, from a venous sample collected at the time of presentation with urticarial lesions.

Autologous serum skin test was performed in cases only. It was performed with 0.05 ml of the patient’s undiluted serum after blood centrifugation, which was injected intradermally into the volar aspect of the forearm together with a simultaneously injected equal volume of normal saline as control at an adjacent site. A red weal with a diameter of 1.5 mm greater than that at control site at 30 min was considered as positive.

2.1. Statistical analysis

Whole data were assimilated in the form of a master chart. Quantitative data were analysed by using a one way analysis of variance (ANOVA) and independent sample t-test. Categorical data were analysed by using the chi-square test. p-Value of <0.05 was considered significant. Data were subjected to statistical analysis using R-software.

3. Results

The age of the patients in the study group ranged from 8 to 70 yrs with a mean age of 30.07 yrs ± 3.55. Out of the total 194 patients 72 (37.11%) were males and 122 (62.88%) were females. Out of a total of 194 patients, 67 patients had a positive ASST, accounting for 34.53% of the total patients of

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of weals</td>
<td>None</td>
<td>≤10</td>
<td>11–50</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Size of weals</td>
<td>None</td>
<td>&lt;1cm</td>
<td>1–3 cm</td>
<td>&gt;3 cm</td>
</tr>
<tr>
<td>Intensity of pruritis</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Duration</td>
<td>None</td>
<td>&lt;1 h</td>
<td>1–12 h</td>
<td>&gt;12 h</td>
</tr>
<tr>
<td>Frequency of appearance</td>
<td>None</td>
<td>One in a week</td>
<td>2–3 times per week</td>
<td>Daily</td>
</tr>
<tr>
<td>Frequency of drug intake</td>
<td>None</td>
<td>One in a week</td>
<td>2–3 times per week</td>
<td>Daily</td>
</tr>
</tbody>
</table>
chronic urticaria, as compared to 127 with a negative test. Total urticaria severity score (TUSS) was higher in ASST positive subjects (12.7607) than in ASST negative ones (10.2671). The difference was statistically significant ($p = 0.041$). The difference in MPV levels between the cases with positive ASST, negative ASST and controls was statistically significant (Table 2). MPV levels showed a positive correlation with severity of chronic urticaria (Table 3).

The mean platelet count in ASST positive subjects was $2.04383 \pm 1.820685$ as compared to $2.04200 \pm .647276$ and $1.83170 \pm .860361$ in ASST negative and controls groups, respectively (Table 4). The count was higher in ASST positive group as compared to the other two groups but it had no statistical significance ($p1 = .994$, $p2 = .277$, $p3 = .327$). The correlation between severity and platelet count was also not statistically significant ($r = 0.074$; $p = 0.454$).

4. Discussion

Urticaria is a common disease, characterised by distinct skin reaction pattern, i.e., the development of short-lived itchy weals. Chronic urticaria may be ordinary, physical or vasculitic, but the term is often considered synonymous with the ordinary presentation of chronic urticaria. In some it is not possible to ascertain a specific aetiology, thus termed chronic ‘idiopathic’ urticaria. Autoimmunity has been implicated in a large subset of these patients but it might not be the only cause. Recent studies support the involvement of additional pathogenic mechanisms in patients with chronic urticaria. The activation of a coagulatory cascade and systemic inflammatory processes has been investigated and implicated in the pathogenesis of chronic urticaria.

In our study, mean platelet volume, an indicator of platelet activity and thus extrinsic coagulation pathway, was assessed in all three groups, i.e., cases with a positive ASST, negative ASST and controls. Higher levels of MPV were found in ASST positive than ASST negative and controls (12.72607 fl) (7.61313 fl) and controls (7.95 ± 1.08 and 7.72 ± 1.04 fl) respectively. The results were statistically significant ($p1 = .039$, $p2 = .007$ and $p3 = .39$). There was also a significant positive correlation between the severity of chronic urticaria and mean platelet volume in ASST positive patients ($r = 0.414$; $p = 0.007$).

The difference in mean platelet volume between the three groups was statistically significant.

Table 2
Mean platelet volume in different groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Value (fl)</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASST+</td>
<td>12.72667 ± 1.876425</td>
<td>$p1 = 0.012$ (Sig)</td>
</tr>
<tr>
<td>ASST−</td>
<td>10.32556 ± 1.898271</td>
<td>$p2 = 0.015$ (Sig)</td>
</tr>
<tr>
<td>Controls</td>
<td>10.01313 ± 2.312550</td>
<td>$p3 = 0.194$ (NS)</td>
</tr>
</tbody>
</table>

$p1$, $p$-Value between ASST+ CU and ASST− CU. $p2$, $p$-Value between ASST+ CU and controls. $p3$, $p$-Value between ASST− CU and controls.

Table 3
Correlation of severity of chronic urticaria with MPV.

<table>
<thead>
<tr>
<th>TUSS</th>
<th>TUSS</th>
<th>MPV</th>
<th>Pearson correlation</th>
<th>Sig (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.414*</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MPV levels showed a positive correlation with severity of chronic urticaria.

* Correlation is significant at the 0.01 level (2-tailed).
positive patients only ($r = 0.44; p < 0.001$) but not in ASST negative ones (Magen et al., 2010).

Our results were also comparable to that of Cohen et al. High mean platelet volume was the most common abnormal laboratory finding in patients with chronic urticaria. Out of 12,778 patients with chronic urticaria 3552 had raised MPV levels. 31% of women and 23% of men had significantly higher mean platelet volume as compared to controls (Cohen et al., 2012).

Similar results were seen by Chandrashekar et al. who observed significantly higher mean platelet volume and platelet distribution width in patients with CU when compared to controls (Cohen et al., 2012).

The difference in mean platelet volume observed in our study cannot be fully explained due to the paucity of literature on this issue, but it points either towards a direct role of platelet mediators in the pathogenesis of chronic urticaria or simply reflects bone marrow stimulation, which may be induced by systemic inflammation or as a result of increased consumption of platelets at the site of urticarial weals.

The assumption that platelet mediators might play a direct role in the pathogenesis of chronic urticaria, is supported by the recent reports proposing the activation of a coagulation cascade in chronic urticaria. Asero et al. observed that chronic urticaria patients have a positive autologous plasma skin test (86%) more commonly than a positive autologous serum skin test (53%) (Asero et al., 2006). This suggests a possible role of plasma clotting factors. This was further confirmed by Asero et al. (2008), Takahagi et al. (2010) and Takeda et al. (2011) who reported significantly elevated mean prothrombin fragments F1+2, factor VIIa and D-dimer levels in patients of chronic urticaria than in controls. A correlation with severity was also observed. However, this view was contradicted by Metz et al. who found that skin reactivity to autologous blood is largely unaffected by the presence or absence of coagulative abnormalities (Metz et al., 2009).

It is thus suggested that platelets might be the activators of an extrinsic coagulation pathway in these cases and may in turn influence the histamine releasing effector cells and thus the disease and its activity.

Besides coagulation and thrombosis, platelets also produce a large number of substances that are crucial mediators of inflammation. Recent studies also report a correlation between a higher MPV and active inflammatory response. Milovanovic et al. (2004) and Yazici et al. (2010) found that MPV correlated with disease activity and response to treatment in rheumatoid arthritis. Canpolat et al. (2010) found that MPV levels were positively correlated with psoriasis area and severity index score and disease duration. It was also significantly increased in those with arthritis than those without (Canpolat et al., 2010). Purnak et al. found that MPV correlated with disease activity and remission on adherence to gluten free diet in coeliac disease (Purnak et al., 2011).

### Table 4

<table>
<thead>
<tr>
<th>Group</th>
<th>Value</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASST+</td>
<td>2.04383 ± 1.820685</td>
<td>$p_1 = 0.994$ (NS)</td>
</tr>
<tr>
<td>ASST−</td>
<td>2.04200 ± 0.647276</td>
<td>$p_2 = 0.277$ (NS)</td>
</tr>
<tr>
<td>Controls</td>
<td>1.83170 ± 0.860361</td>
<td>$p_3 = 0.327$ (NS)</td>
</tr>
</tbody>
</table>

$p_1$, $p$-Value between ASST+ CU and ASST− CU.

$p_2$, $p$-Value between ASST+ CU and controls.

$p_3$, $p$-Value between ASST− CU and controls.
It is thus suggested that chronic urticaria is a part of the spectrum of immune mediated inflammatory diseases. The systemic inflammatory response thus associated, induces bone marrow stimulation and production of larger platelets.

The possibility of bone marrow stimulation secondary to increased consumption of platelets at the site of urticarial weals cannot be explained as no significant differences in platelet counts were observed between the groups.

We hereby conclude that autoimmune urticaria, a clinically more severe disease, is characterised by low-grade inflammation and platelet activation. Thus coagulation and inflammatory cascades may play a positive role in the pathogenesis of chronic urticaria, paving the way for better understanding of the disease and introduction of newer drugs.

Conflict of interest

None.

References


