The effect of disease control on mean platelet volume and red blood cell distribution in patients with acromegaly

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Abstract: Objectives: Several studies have shown increased atherogenic risk factors and biomarkers of inflammation and atherosclerosis in association with growth hormone excess. Mean platelet volume (MPV) and red blood cell distribution (RDW) are currently gaining interest as new independent cardiovascular risk factors. The aim of this study was to evaluate the effect of disease control on MPV and RDW in acromegaly patients. Materials and methods: We retrospectively enrolled 36 acromegaly patients (23 males, 13 females; mean age 41.94 ± 11.55). Patients were divided into two groups: disease controlled by surgical treatment alone (group A) or by somatostatin analog (SSA) therapy (group B). MPV and RDW measurements were evaluated during active and inactive disease periods in the two groups. Results: There were statistically significant increases in MPV and RDW in patients receiving SSA therapy (P = 0.012 and P = 0.020, respectively). The differences in MPV and RDW changes in patients receiving surgical treatment alone were not statistically significant (P=0.364 and P=0.339, respectively). Conclusions: This is the first report on the evaluated the effect of disease control on MPV and RDW in acromegaly patients. Our study results showed that MPV and RDW measurements are significantly increased in acromegaly patients with disease controlled by SSA therapy. Therefore, acromegalic patients treated with SSAs may have increased cardiovascular risk based on an increase in MPV and RDW.

Keywords: Acromegaly, inflammation, cardiovascular risk, somatostatin

Introduction

Acromegaly is a disease caused by growth hormone (GH) hypersecretion from a pituitary adenoma. IGF-I acts as a mediator of the GH effects. Cardiac effects of acromegaly are left ventricular hypertrophy, impaired cardiac systolic and diastolic function, arrhythmias, conduction abnormalities, valvular heart disease, and ischemic heart disease. Acromegaly is associated with a 2 to 2.5 times increased mortality risk [1]. Mortality evaluations show that approximately 60% of patients with acromegaly die from cardiovascular disease [2, 3]. Pituitary surgery is the primary treatment for acromegaly patients. In most patients, medical therapy [somatostatin analogs (SSAs), dopamine agonists, and a GH receptor antagonist] and radiotherapy are used as adjuvant treatment in the setting of persistent disease despite surgical intervention [1]. With disease control, left ventricular hypertrophy and function may improve, dilated cardiomyopathy may reverse, and endothelial dysfunction may improve [1].

Some previous studies have found an increase in inflammation markers such as tumour necrosis factor (TNF)-α, interleukin (IL)-8, intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 in patients with acromegaly [4, 5]. Chronic inflammation plays an important role in the pathogenesis of atherosclerosis [6]. Mean platelet volume (MPV) and red blood cell distribution (RDW) are simple markers of inflammation that can be
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easily obtained from the complete blood count (CBC) test, and are gaining interest as new independent cardiovascular risk factors [7-19]. These markers are an indicator of the overall inflammatory status of the body [20, 21] and an alteration in these parameters may be found with disease control in acromegaly.

Only a few, brief reports have investigated so far the relationship between MPV and acromegaly, with contrasting results [7, 22, 23]. However, the effect on MPV and RDW of disease control in acromegaly has not been studied. Thus, the aim of the current study was to evaluate MPV and RDW changes in disease controlled by surgical treatment alone or by SSA therapy in patients with acromegaly.

Materials and methods

Subject

We retrospectively enrolled 36 acromegalic patients (23 males, 13 females; mean age 41.94 ± 11.55, between 23 and 78 years old). 35 patients underwent surgery and one patient received long-acting SSAs as primary therapy (one did not consent to surgery). The cases in the study were categorized in two groups. 12 patients did not require any medical therapy after surgery because remission could be maintained without adjuvant treatment (group A) and 24 patients achieved remission with long-acting SSA treatment (group B).

For each patient, we evaluated simultaneous measurements of MPV, RDW, IGF-I and fasting plasma glucose (FPG) and comorbid conditions such as diabetes mellitus (DM) and hypertension (HT) for active and inactive disease periods from the electronic patient database in our hospital. Also, total disease duration and tumor size at the time of diagnosis were recorded for the patients. Data for periods of active disease contained information for newly diagnosed and untreated patients. Data for periods of inactive disease included data from the last visit of patients with inactive disease. The criteria used to define inactive disease were nadir GH < 1 μg/L after 75 g OGTT and normal agematched IGF-I levels [1].

Patients with known hematologic or chronic inflammatory diseases, initially any pituitary hormone deficiency or any pituitary hormone insufficiency developing during the disease period, patients receiving another medical treatment outside SSAs for disease control, patients who did not have a CBC test in the period of active disease, and those who still had active disease were excluded from the study. Also, CBC investigations made during any active infection were not included in the study.

The study protocol was approved by the local ethics committee. The requirement for patient informed consent was waived.
Laboratory analysis

MPV (normal range, 7.0 to 11.0 fl.) and RDW (normal range, 11.8% to 14.6%) were routinely measured as part of the automated CBC using a hematology analyzer (Coulter Hmx; Beckman Coulter [UK] Ltd, High Wycombe, Bucks, UK). Serum glucose levels were measured using a hexokinase enzymatic method (Architect c8000 Chemistry Analyzer, Abbott Diagnostics, IL, USA) according to the manufacturer’s instructions. Serum GH was assessed by electrochemiluminescence immunoassay (ECLIA) (hGH kit, Architect c8000 Chemistry Analyzer, Abbott Diagnostics, IL, USA). Serum total IGF-1 was assessed by immunometric chemiluminescence assay (IMMULITE 2000, SIEMENS, USA). Age-adjusted reference ranges were used for evaluation of IGF-I levels.

Statistical analysis

Descriptive statistics of studied variables (characteristics) are presented as mean and standard deviation for continuous variables and as count and percent for categorical variables. Student t test was used to compare Group A and Group B means. In addition, Paired t test was used to compare before and after treatment values. Comparisons of proportions were done by Z test. Statistical significance levels were considered as 5% and the SPSS (version 13.0) statistical program was used for all statistical computations.

Results

Following retrospective screening of 75 patients with acromegaly, 39 patients were excluded, therefore 36 patients were included in the present study (23 males and 13 females patients). A detailed description of how the patients were selected is presented in Figure 1.

Table 1. Demographic characteristics of study subjects

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=12)</th>
<th>Group B (n=24)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)*</td>
<td>46.50 ± 14.53</td>
<td>39.67 ± 9.27</td>
<td>0.095</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>8/4</td>
<td>15/9</td>
<td>0.804</td>
</tr>
<tr>
<td>Tumor size (mm)*</td>
<td>19.55 ± 12.71</td>
<td>21.74 ± 12.49</td>
<td>0.645</td>
</tr>
<tr>
<td>Disease duration (year)*</td>
<td>3.56 ± 2.77</td>
<td>6.67 ± 3.93</td>
<td>0.020</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>0</td>
<td>9</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Data are expressed as mean ± SD for normally distributed data.

Presence of DM and HT, IGF-I, FPG, MPV, RDW, white blood cell counts (WBC), hemoglobin (Hb) and platelet (PLT) measurement data for active and inactive disease periods in the study groups are shown in Table 2. Serum IGF-1 levels were significantly decreased in patients in group A (P = 0.001) and Group B (P = 0.001) with disease control. There were no statistically significant differences in prevalence of DM, HT and FPG, WBC, Hb and PLT measurements between active and inactive disease periods for both groups. MPV and RDW measurements were statistically significantly higher for the inactive disease period compared to the active period in patients in group B (8.07 ± 1.23 vs 8.57 ± 1.36, P = 0.012 and 13.51 ± 1.17 vs 14.15 ± 1.48, P = 0.020, respectively). There were no significant differences for MPV and RDW between active and inactive disease periods for patients in group A (P = 0.364 and P = 0.339, respectively).

When we analyzed IGF-I, FPG, MPV, RDW, WBC, Hb and PLT measurements and the presence of DM and HT between the two study groups separately in active and inactive disease periods, we found that IGF-I, MPV, RDW, WBC, Hb and PLT measurements and the prevalence of DM and HT were not significantly different between the groups (Table 3). The mean FPG levels were significantly higher in group B compared to group A for the inactive disease period (96.04 ± 11.79 vs 87.50 ± 8.39, P = 0.032), while mean FPG was similar between the groups for the active disease period.

Discussion

Cardiovascular morbidity and mortality are increased in acromegaly. Nevertheless, it is unclear whether this is related to increased conventional risk factors or whether it is a result of the direct effect of GH excess on cardiovascular function [3]. On the other hand, it is
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Table 2. Demographic and laboratory data for active and inactive disease periods in the study groups

<table>
<thead>
<tr>
<th></th>
<th>Group A (n =12)</th>
<th>Group B (n=24)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of DM</td>
<td>1/12</td>
<td>1/12</td>
<td>1.000</td>
</tr>
<tr>
<td>Presence of HT</td>
<td>2/12</td>
<td>2/12</td>
<td>1.000</td>
</tr>
<tr>
<td>IGF-1(ng/ml)*</td>
<td>791.58 ± 321.38</td>
<td>254.8 ± 77.23</td>
<td>0.001</td>
</tr>
<tr>
<td>FPG (mg/dl)*</td>
<td>106.33 ± 42.16</td>
<td>87.50 ± 8.39</td>
<td>0.103</td>
</tr>
<tr>
<td>MPV (fl )*</td>
<td>8.56 ± 1.83</td>
<td>8.41 ± 1.61</td>
<td>0.364</td>
</tr>
<tr>
<td>RDW (%)*</td>
<td>13.33 ± 0.61</td>
<td>13.42 ± 0.63</td>
<td>0.339</td>
</tr>
<tr>
<td>WBC (10^3/μL)*</td>
<td>6.61 ± 1.63</td>
<td>6.76 ± 1.60</td>
<td>0.658</td>
</tr>
<tr>
<td>Hb (g/dl)*</td>
<td>14.25 ± 1.19</td>
<td>14.78 ± 1.15</td>
<td>0.191</td>
</tr>
<tr>
<td>PLT (10^3/μL)*</td>
<td>235.67 ± 50.00</td>
<td>218.08 ± 29.65</td>
<td>0.170</td>
</tr>
</tbody>
</table>

*Data are expressed as mean ± SD for normally distributed data. DM: Diabetes mellitus; HT: Hypertension; IGF-1: Insulin-like growth factor 1; FPG:Fasting plasma glucose; MPV: Mean platelet volume; RDW: Red blood cell distribution; WBC: White blood cell counts; Hb: Hemoglobin; PLT: Platelet

now widely accepted that the development of atherosclerotic lesions involves a chronic inflammatory response [6]. MPV and RDW have shown a relationship with inflammation [20, 21], and the relationship between MPV and RDW elevation and increased cardiovascular risk has been shown in various studies [8-19].

Arikan et al. [4] found that serum TNF-α and IL-8 levels were significantly higher in newly diagnosed acromegalic patients than in controls. In a recent study that examined markers of early atherosclerosis, significantly decreased flow mediated dilatation, increased carotid intima media thickness and epicardial adipose tissue thickness were found in patients with active acromegaly compared to controls [24]. The results of these two studies [4, 24] imply a possible association between acromegaly and both atherosclerosis and inflammation. Also, in another study recently published, Topaloglu et al. [5] demonstrated that epicardial fat thickness (EFT) was significantly increased, aortic strain (AoS) and aortic distensibility (AoD) were significantly decreased, and serum ICAM-1 and VCAM-1 levels were significantly higher in acromegaly patients compared to controls. On the other hand, there were no significant differences in EFT, AoD, AoS, and serum CAMs between active and inactive acromegaly patients in this study [5]. The results of this study support the hypothesis that the risk of atherosclerosis does not decrease and chronic inflammation continues despite disease control in acromegaly.

Ersoy et al. [22] reported that when MPVs were compared, no significant differences were detected between patients with acromegaly and a control group (8.90 ± 1.48 vs 8.81 ± 1.26, P>0.05), however, a significant decrease in MPV was observed following six months of treatment with SSAs (8.93 ± 1.25 vs 8.49 ± 1.21, P<0.05). Likewise, Durmaz et al. [23] reported that serum MPV levels in active acromegalic patients were not different from control subjects before treatment with SSAs (7.9 ± 0.8 and 7.9 ± 0.9 fl, respectively). However, contrary to the findings of Ersoy et al., Durmaz et al. found significantly increased serum MPV values in acromegalic patients after SSA treatment (7.9 ± 0.8 vs 8.3 ± 0.9 fl, P = 0.047). Also, a recent study showed that MPV was significantly higher in an active acromegaly group compared to a control group (9.68 ± 1.11 vs 8.53 ± 1.18, P = 0.004) [7]. As shown in these three studies, there are conflicting results with regard to MPV measurements in active acromegaly patients and MPV changes in acromegaly patients receiving SSAs [7, 22, 23]. However, so far no report has investigated the relationship between RDW and acromegaly. To the best of our knowledge, our present study is the first study evaluating MPV and RDW changes with disease control for patients with acromegaly, comparing surgical treatment alone and SSA therapy.

In our study, MPV and RDW were found to be significantly higher in the inactive disease period compared to the active disease period in patients with disease controlled by SSA therapy (group B). MPV and RDW were not significantly different between the remission and active periods for patients with disease controlled by
surgical treatment alone (group A). However, when we analyzed MPV and RDW measurements between the two study groups separately in active and inactive disease periods, we found that the MPV and RDW measurements were not significantly different in group B compared with group A for the inactive disease period while FPG levels were significantly higher in group B compared with group A for the active disease period (Table 3). There are some studies showing that SSAs have implications for thrombocytopenia and decreased platelet aggregation, nevertheless, there are studies showing no effect on platelet function [25, 26, 27]. As mentioned above, there are conflicting results for the effect on MPV of SSA treatment [22, 23]. In fact, the explanation of such findings of MPV and RDW enhancement with SSAs are not straightforward. This condition can be partly explained by mean FPG levels being significantly higher in group B compared with group A for the inactive disease period, since the previous study showed that the positive correlation between RDW and MPV increased with elevated plasma glucose levels, even for normoglycemic individuals [28-30]. The results of our study suggest that acromegalic patients receiving SSA treatment have an increased risk of atherosclerosis, although the disease is under control, since MPV and RDW enhancement were associated with an increased risk of atherosclerosis [8-19]. Also, patients with disease controlled by surgical treatment alone lack a significant alteration of MPV and RDW, although a minimal reduction in MPV supports the idea that there is no direct relationship between IGF-1 or GH levels and MPV or RDW measurements.

Another finding of our study was that there were nine patients treated with Gamma Knife in group B while no Gamma Knife treated patients were in the group A. This should not be surprising since radiotherapy is used as an adjuvant treatment in the setting of persistent disease despite surgical intervention [1]. However, as previously mentioned, patients who had any pituitary hormone insufficiency developed during the disease period were excluded from the study. Thus, even if there were patients treated with radiotherapy only in the control group, this would not be expected to affect our results. Additionally, total disease duration was higher in patients in group B compared to Group A (6.67 ± 3.93 vs 3.56 ± 2.77). This finding can be explained by the gradual increase of surgical experience in recent years.

There are some limitations to our study. Firstly, BMI and blood pressure measurements were not assessed to compare active and inactive disease periods since our study had a retrospective design. It is possible that BMI and blood pressure changes may affect MPV and RDW measurements. Secondly, relationships between MPV or RDW and atherosclerosis markers such as pulse wave velocity, carotid intima-media thickness, arterial stiffness index or augmentation index were not obtained in this study.
Conclusions

The evaluation of MPV and RDW changes in disease controlled by surgical treatment alone or by SSA therapy in patients with acromegaly showed that acromegalic patients who received SSA treatment had increased MPV and RDW. These findings may indicate an association between SSA treatment and an increase in cardiovascular risk. Based on these data, we recommend strict clinical follow-up of acromegalic patients receiving SSA treatment in terms of atherosclerotic disease. Further well-designed trials that include other atherosclerotic markers are warranted to confirm this association.

Disclosure of conflict of interest

None.

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References


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