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Original Article

The Relationship Between Premature Adrenarche and Markers of Inflammation in Complete Blood Count

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ABSTRACT

Aim: Premature adrenarche (PA) has been associated with metabolic and polycystic ovary syndrome (PCOS) and, thus, with an increased risk for type 2 diabetes and cardiovascular diseases in later life. Mean platelet volume (MPV), neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) are parameters used to show inflammation. This study planned to evaluate systemic inflammation in children with PA using MPV, NLR, and PLR.

Materials and Methods: The study included 40 female patients diagnosed with PA and 40 healthy female individuals as a control group. The patient and control groups' MPV, NLR, and PLR values were compared.

Results: The mean age of the PA group was 7.18±0.66 years, and the mean age of the control group was 7.09±1.08 years. The mean MPV and platelet distribution width (PDW) values in the PA group were significantly higher than those in the control group (10.25±0.87 vs 9.52±0.79, p<0.001 and 15.43±1.31 vs 14.35±1.84, p=0.04, respectively). However, in the PA group, NLR and PLR were not significantly different from the values in the control group (p>0.05). The results of multivariate logistic regression analysis revealed that the MPV [odds ratio (OR); 95% confidence interval (CI): 0.331 (0.174-0.630); p=0.001], and PDW [OR; 95%: CI: 0.612 (0.425-0.884); p=0.008] were associated with PA in the patient group.

Conclusion: Our results demonstrated that PA patients had significantly higher MPV levels and PDW than the healthy controls. Hence, recognition of early markers in adolescence might reveal primary pathogenetic alterations predictive of the later development of PCOS and/or metabolic syndrome.

Keywords: Premature adrenarche, mean platelet volume, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, cardiovascular diseases, inflammation

Introduction

Adrenarche represents a pivotal stage in adrenal cortex development, heralding an upsurge in adrenal androgen precursors. This transformative process typically unfolds in mid-childhood, around 5-8 years old in humans (1). Central to assessing adrenarche are key serum markers such as dehydroepiandrosterone (DHEA) and DHEA sulfate conjugate (DHEAS) (2). While the adrenocorticotropic hormone plays a pivotal role, intrinsic and external factors can influence adrenal androgen (AA) secretion, necessitating a holistic understanding (3).

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Premature adrenarche (PA) emerges as a distinctive phase marked by premature androgenic signs before the age of 8 in girls or 9 in boys, coupled with elevated adrenal androgen precursors for their prepubertal age (4,5). In recent times, the spotlight on PA has intensified, linking it to factors such as small birth size, metabolic concerns, and polycystic ovary syndrome (PCOS) (6). This correlation raises concerns about heightened risks of cardiovascular diseases (CVD) and diabetes later in life (7,8). Early puberty has also been associated with increased body mass index (BMI) and heightened obesity risks in women in adulthood (8).

Shifting our focus to hemostasis and thrombosis, platelets, which are pivotal in these processes, have their function influenced by factors such as platelet size (9). Mean platelet volume (MPV), easily measurable in a complete blood count, has emerged as an indicator of platelet size. Recent studies hint at its potential association with chronic diseases such as diabetes and CVD. Increased MPV has been shown to correlate with elevated risks of adverse cardiovascular events, mortality in acute coronary syndrome patients, and occurrences of hypertension and ischemic stroke in the general population (10,11). Additionally, parameters derived from the complete blood count, such as the platelet/lymphocyte ratio (PLR) and the neutrophil/lymphocyte ratio (NLR), indicate inflammation and have been reported to rise in various metabolic and endocrinological conditions (12,13).

Despite the significance of PA, studies exploring its long-term cardiovascular risk profiles and adult outcomes are rare (7,8). Understanding the impact of PA on MPV may provide valuable insights into potential early markers of cardiovascular risk in this population, paving the way for targeted interventions and improved management strategies in order to mitigate long-term health implications. This study endeavored to bridge this gap by investigating MPV, NLR, and PLR in patients with PA, so as to give insights into their relationship to cardiovascular risks and overall health outcomes.

Materials and Methods

Study Population and Data Collection

A meticulous retrospective examination of the medical records of 40 female patients diagnosed with PA at İzmir Bakırçay University Çiğli Training and Research Hospital between January, 2022 and December, 2023 was carried out. Ethical approval, aligning with the Declaration of Helsinki, was obtained from the İzmir Bakırçay University Non-invasive Clinical Research Ethics Committee (approval no.: 1239, dated: 10.18.2023). Informed consent, acknowledging the study's objectives and potential medical data publication, was secured from the parents of all of the patients.

The inclusion criteria were females diagnosed with PA between 6 and 8 years of age, excluding those showing clinical signs of adrenal androgen activity before the age of 8. DHEAS values of >40 µg/dL were considered adrenarche (14). The control group comprised healthy children matched for age and gender during routine health visits. Auxological data calculations were carried out using an automated calculator (15). A consistent pediatric endocrinologist, adhering to Tanner's criteria (16), assessed pubertal status, while bone age was determined by referencing Greulich and Pyle's Radiographic Atlas of Skeletal Development.

Various parameters were analyzed, including complete blood count results, luteinizing hormone, DHEAS, estradiol, total testosterone, lipid profile, and procalcitonin. Hormone levels were assessed through the chemiluminescence method utilizing a Beckman Coulter DxI® 600 analyzer. Automated devices, specifically the Technicon H-1 System from Technicon Co, Tournai, Belgium, were employed to obtain erythrocyte indices, platelet counts, and MPV values. Complete blood count measurements also provided the number of leukocytes, lymphocytes, neutrophils, platelets, MPV, and platelet distribution width (PDW). The determination of the NLR entailed the division of the neutrophil count by the lymphocyte count, and for the PLR, the platelet count was divided by the lymphocyte count.

Statistical Analysis

The analysis of data was carried out using SPSS for Windows, version 25.0 (IBM Inc., Armonk, NY, USA), providing a robust platform for comprehensive data exploration. Group comparisons were executed utilizing the independent samples t-test for variables conforming to normal distributions, while the Mann-Whitney U test was employed for distributions with skewed data. The significance threshold was set at $p<0.05$, signifying statistical significance, and no adjustments were made for multiple statistical tests, ensuring a nuanced interpretation of the findings.

Results

The patient cohort included forty females diagnosed with PA, while the control group comprised forty healthy girls. The PA group's mean age was 7.18±0.66 years; and in the healthy control group, it was 7.09±1.08 years. The demographic characteristics of the PA patients are given

in Table I. Notably, 26.3% of these patients exhibited pubic hair, 16.3% displayed axillary hair, 6.3% had adult-type body odor, and 1.3% presented with acne. No family history of PA was reported among the patients. BMI standard deviation scores of 5 patients were ≥2. During examination, 62.5% of the patients displayed axillary hair growth. Tanner staging indicated that 12.5% were at stage 1, 25% were at stage 2, and 12.5% were at stage 3 for pubic hair growth, with all patients being at stage 1 for breast development.

The laboratory findings for the PA patients, outlined in Table II, included a median bone age of 7.8 (5-10.5) years. The median difference between chronological and bone age was 0.86 (-1.89-3.34) years.

Complete blood count parameters in Table III revealed no significant differences between the groups regarding red blood cell count, white blood cell count, hemoglobin and hematocrit levels, mean erythrocyte volume, red cell distribution width, or platelet count (p>0.05). However, MPV and PDW values were significantly higher in the PA group compared to the control group (p<0.001 and 0.04, respectively). In contrast, PLR and NLR did not show any significant differences between the two groups (p>0.05).

Results from multivariate logistic regression analysis indicated that MPV [odds ratio (OR); 95% confidence interval (CI): 0.331 (0.174-0.630); p=0.001] and PDW [OR; 95% CI: 0.612 (0.425-0.884); p=0.008] were associated with PA in the patient group.

Table I. The demographic characteristics of premature adrenarche patients

Characteristics	Premature adrenarche patients (n=40)
Height SDS	1.11±1.23
Weight SDS	0.73±1.22
Body mass index SDS	0.85±1.11
Systolic blood pressure percentile	49.93±26.07
Diastolic blood pressure percentile	61.31±20.08

SDS: Standard deviation score

Table II. The laboratory findings of the premature adrenarche patients

Characteristics	Premature adrenarche patients (n=40)
HOMA-IR	1.78±1.13
HDL cholesterol (mg/dL)	53.05±10.03
LDL cholesterol (mg/dL)	86.62±20.32
Triglyceride (mg/dL)	75.25±33.34
LH (mlU/mL)	0.3 (0.03-0.8)
FSH (mlU/mL)	1.29±0.69
Estradiol (pg/mL)	5 (5-18.4)
DHEAS (µg/dL)	85.84±41.25
Procalcitonin (ng/mL)	0.03 (0.01-0.11)

HOMA-IR: Homeostasis Model Assessment Insulin Resistance, HDL: High density lipoprotein, LDL: Light density lipoprotein, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, DHEAS: Dehydroepiandrosterone-sulfate

Table III. Complete blood parameters in the premature adrenarche and control groups

	Premature adrenarche group (n=40)	Control groups (n=40)	p value
WBC (/µL)	7,198.25±1,987.32	7,029.5±1,612.42	0.678
RBC (×10⁶/µL)	4.88±0.06	4.94±0.06	0.357
HGB (g/dL)	12.99±0.10	12.91±0.21	0.461
HCT (%)	38.76±0.34	39.01±0.11	0.654
MCV (fL)	80.16±0.23	80.28±0.36	0.823
RDW (%)	13.54±0.09	13.42±0.11	0.654
PLT (/µL)	328,300±80,921	330,650±76,577	0.894
MPV (fL)	10.25±0.87	9.52±0.79	**<0.001**
PDW (%)	15.43±1.31	14.35±1.84	**0.004**
NLR	1.42±1.17	1.30±0.58	0.562
PLR	113.01±34.69	113.22±31.79	0.977

WBC: White blood cell, RBC: Red blood cell, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean erythrocyte volume, MCH: Mean erythrocyte hemoglobin, MCHC: Mean erythrocyte hemoglobin concentration, RDW: Red cell distribution width, PLT: Platelet, MPV: Mean platelet volume, PDW: Platelet distribution width, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio

Correlation analysis revealed a weak positive correlation between MPV and PDW (r=0.252, p=0.024) and a moderate correlation between NLR and PLR (r=0.435, p<0.001). However, no correlations were detected between MPV, NLR, PLR, and DHEAS levels.

Discussion

In this study, we investigated the correlation between inflammatory markers in a complete blood count and PA. Our findings indicated that individuals with PA exhibited significantly elevated levels of MPV and PDW compared to their healthy counterparts. This investigation was prompted by the understanding that PA represents an early stage in the development of metabolic syndrome and PCOS. Thus, identifying early markers in adolescence might reveal fundamental pathogenetic alterations predictive of later PCOS and/or metabolic syndrome development.

MPV, a parameter gauging the average platelet size in the blood, has been extensively studied for its potential role in assessing and predicting CVD risk, particularly in patients with acute coronary syndrome (10,11). Girls with a history of PA often experience a hyperandrogenic hormonal environment, potentially heightening their cardiovascular risk (17). An earlier study highlighted initial subclinical deterioration in cardiac function and atherosclerotic changes among girls with PA. The authors indicated that PA elevated the likelihood of coronary heart disease, which was attributed to heightened epicardial adipose tissue and carotid intima-media thickness measurements in individuals with PA (18). The augmented risk of coronary heart disease in children with PA was linked to excess adipose tissue in adulthood, suggesting that a process which begins with childhood obesity may contribute to CVD later in life, alongside PA and adult obesity (19). Bolat et al. (20) explored the relationship between platelet aggregation and PA, reporting increased collagen-induced platelet aggregation in girls with PA, potentially associated with an elevated risk of CVD. Moreover, a significant number of girls with a history of PA later develop findings of PCOS, including hyperandrogenism, anovulatory menstrual cycles, and insulin resistance (21). Coviello et al.'s (22) recent findings indicated that adolescents with PCOS exhibited a notably higher occurrence of metabolic syndrome components in comparison to their healthy peers, suggesting a potential relationship between CVD and PA, which carries a high risk of developing PCOS. Our results aligned with these associations, revealing significantly higher levels of MPV and PDW in individuals with PA - both potential inflammation markers for assessing and predicting CVD risk - when compared to healthy controls. However, the PLR and the NLR, recognized as potential inflammation markers for cardiac and non-cardiac diseases in recent years (23), were similar between our study group and our healthy controls.

Prepubertal children with PA commonly develop hyperinsulinemia. Consistent with other research, Liimatta et al. (8) demonstrated that insulin resistance persists into young adulthood in women with a history of PA. Their study revealed that the risk of impaired glucose metabolism persists into adulthood and is strongly associated with central obesity (8). Ibáñez et al. (24) reported similar findings in oral glucose tolerance tests (OGTT) among Catalan girls with premature pubarche. Despite being mostly lean, there was an observed increase in central fat mass associated with hyperinsulinemia (24). In contrast, in a study by Meas et al. (25) where girls with premature pubarche and control subjects within normal BMI limits completed OGTTs, it was found that there was normal glucose tolerance in all subjects, with no significant differences in the plasma glucose or serum insulin profiles between the study groups (25). In our study, insulin resistance in girls with PA was evaluated when measured by HOMA-IR, and no significant increase in insulin resistance was detected.

Study Limitations

Acknowledging this study's limitations provides context for interpreting the findings and guides future research endeavors. The inclusion of a relatively small sample size from a single institution may restrict the generalizability of the findings to the broader population. Additionally, since the number of male patients with PA was insufficient, only female cases were included in this study. This study's cross-sectional nature hinders establishing a cause-and-effect relationship between PA and the observed markers of inflammation. Cross-sectional studies offer associations but need to elucidate the temporal sequence of events. Continued research with larger cohorts and longitudinal designs will enhance the robustness of our understanding of PA and its cardiovascular implications**.**

Conclusion

In summary, this study provides a foundational framework to investigate deeper into the complex interplay between PA and cardiovascular well-being. The highlighted inflammatory markers, notably MPV and PDW, present promising avenues for early risk assessment and targeted interventions. As ongoing research advances our understanding of the intricate mechanisms connecting adrenal androgen production to cardiovascular outcomes,

there is potential for uncovering more nuanced insights. These revelations, in turn, could inform the development of preventive strategies and tailored healthcare approaches for those individuals dealing with PA. Moreover, the correlations observed between MPV and PDW underscore the potential interconnectedness of these markers in the context of PA. This research lays the groundwork for prospective studies which may reveal the complexities of these relationships, offering valuable insights into refining cardiovascular risk management strategies in this specific population.

Ethics

Ethics Committee Approval: Ethical approval, aligning with the Declaration of Helsinki, was obtained from the İzmir Bakırçay University Non-invasive Clinical Research Ethics Committee (dated: 10.18.2023, approval no.: 1239).

Informed Consent: Informed consent, acknowledging the study's objectives and potential medical data publication, was secured from the parents of all of the patients.

Authorship Contributions

Surgical and Medical Practices: F.E., İ.A., Concept: F.E., İ.A., Design: F.E., M.E., Data Collection and/or Processing: M.E., Analysis and/or Interpretation: İ.A., Literature Search: M.E., Writing: F.E., İ.A.

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