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Subclinical inflammation in children with primary hypertension

Introduction:

Arterial hypertension (AH) is found in 4% of children, with primary hypertension (PH) being the predominant cause of high blood pressure from adolescence. The pathogenesis of PH in the developmental age is unclear, and its development is caused by, among other factors, abnormal body composition, a diet rich in sodium, activation of the sympathetic system, early vascular aging, and subclinical inflammation. Experimental studies conducted over the past 25 years and studies in adult patients have shown that immune system activation and subclinical inflammation are essential factors in the initial increase in blood pressure, the persistence of hypertension, and the development of hypertension-mediated organ damage in patients with PH. In adults, elevated inflammatory markers are positively correlated with cardiovascular risk. Inflammation markers have been evaluated in only a few pediatric studies involving small groups of children with PH. There is no conclusive data in the literature on differences in the concentrations of inflammatory markers between children with PH, children with white-coat hypertension (WCH), and healthy children. It has also not been determined which markers differentiate these populations. There is also a lack of information on the relationships between markers of inflammation and adverse cardiac changes, including left ventricular hypertrophy, and between inflammation severity and blood pressure variability in children with PH.

Aims of the study:

1. Comparison of inflammatory markers between untreated pediatric patients with primary hypertension (PH) and healthy children (control group – CG).
2. Comparison of inflammatory markers between untreated pediatric patients with primary hypertension and children with white coat hypertension (WCH).
3. Determination of parameters of subclinical inflammation that may be markers of primary hypertension.
4. To evaluate the relationship between inflammation severity and changes in the heart, including left ventricular hypertrophy, in children with primary hypertension.
5. Determining which inflammatory parameter may be a marker of left ventricular hypertrophy in children with primary hypertension.
6. Determining the relationship between blood pressure variability and inflammation parameters in children with primary hypertension.

Material and methods:

A systematic review of the literature with meta-analysis was conducted in accordance with the PRISMA 2020 and Cochrane recommendations. The MEDLINE, EMBASE, and Cochrane databases were searched up to March 2025. Of the 3076 records, 13 studies published between 2005 and 2024 (745 children with PH and 561 healthy controls) were included in the meta-analysis. Data were analysed using Review Manager, and the risk of bias was assessed using the Newcastle-Ottawa Scale.

The original study included 56 children with PH (15.1±2.3 years), 40 children with WCH (14.7±2.9 years), and 30 healthy children (control group - CG) (14.9±1.4 years). In all patients, the following parameters of inflammation were evaluated: the concentration of high-sensitive C-reactive protein (hsCRP) and interleukin 18 (IL-18) assessed by ELISA (hsCRP: DRG International Inc., IL-18: ThermoFisher Scientific) and the complete blood count-derived parameters (Sysmex XN-1000): neutrophil, lymphocyte, monocyte and platelet counts (1000/μL), mean platelet volume (MPV; fL) and indices: neutrophil-to-lymphocyte (NLR), platelet-to-lymphocyte (PLR), monocyte-to-lymphocyte (MLR), monocyte-to-neutrophile (MNR), and platelet-to-mean platelet volume (PMPVR) [10^{12}/fL] ratios. In all children, I assessed blood pressure by office measurement (Welch Allyn VSM Patient Monitor 300) and ambulatory blood pressure monitoring (Suntech Oscar 2), as well as selected clinical and biochemical parameters. In 34 children with PH, the result of an echocardiographic examination (Philips iE33) was evaluated.

Results:

A systematic review of the literature with meta-analysis found significant differences between children with PH and healthy children in the concentration of hsRCP (MD: 0.07 mg/dL 95CI: 0.04-0.09), the concentration of intercellular adhesion molecule 1 (ICAM-1) (MD: 85.28 ng/mL 95CI: 50.57-119.99), vascular cell adhesion molecule 1 (VCAM-1) (MD: 259.78 ng/mL 95CI: 22.65-496.91), neutrophil count (MD: 0.90 95CI: 0.66-1.14), monocyte count (MD: 0.08 95CI: 0.04-0.11), platelet count (MD: 20.24 95CI: 4.27-36.21), NLR (MD: 0.48 95CI: 0.34-0.62) and LMR (MD: −0.52 95CI: −1, 02–−0.02).

In the first original study, it was shown that hsCRP concentrations were significantly higher in untreated patients with PH compared to CG with no differences between children with PH and WCH (PH vs. WCH vs. GK: 2.9 [1.5-7.3] vs. 1.4 [0.6-6.0] vs. 0.9 [0.5-1.9] [mg/L], p=0.002), neutrophil and monocyte counts were significantly higher in patients with PH and WCH compared to CG: neutrophils (PH vs. WCH vs. CG: 3.89±1.44 vs. 3.40±1.75 vs. 2.63±0.96 [$\times 10^3$/μL], p=0.001), monocytes (PH vs. WCH vs. CG: 0.53 [0.45-0.65] vs. 0.50

[0.40-0.63] vs. 0.44 [0.35-0.53] [$\times 10^3/\mu L$], p=0.026). Analysis of the receiver operating characteristic (ROC) curve showed a good prognostic profile as PH predictors for hsCRP (AUC: 0.668, p=0.0005), neutrophil count (AUC: 0.691, p=0.0001), lymphocyte count (AUC: 0.615, p=0.0230), monocyte count (AUC: 0.622, p=0.0148), and platelet count (AUC: 0.606, p=0.0364), as well as NLR (AUC: 0.619, p=0.0181), MNR (AUC: 0.617, p=0.0204), and PMPVR (AUC: 0.606, p=0.0370). In a multivariate analysis, MLR and platelet count were essential predictors of office diastolic blood pressure(β=0.217, β=0.191), neutrophil count was a predictor for 24-hour systolic blood pressure (β=0.365), MLR, lymphocyte count, interleukin IL-18 and NLR – for 24-hour diastolic blood pressure (β=0.305, β=0.253, β=−0.197, β=−0,189), and neutrophil count and IL-18 – for 24-hour mean arterial pressure (β=0.210, β=−0.209).

In the second original study, in a group of 34 untreated children with PH (15.1±2.1 years, 28 boys, 6girls), left ventricular hypertrophy (LVH) was found in 12 (35.3%) and abnormal relative wall thickness (RWT) in 6 (17.6%) children. Left ventricular diastolic diameter (LVEDd Z-score) correlated negatively with neutrophil count (r=-0.583, p=0.001), NLR (r=-0.562, p=0.002), and positively with MNR (r=0.605, p=0.001), and left ventricular mass index (LVMI [g/m^2]) correlated positively with MNR (r=0.433, p=0.011). RWT correlated positively with neutrophil count (r=0.356, p=0.039) and monocyte count (r=0.378, p=0.027). Patients with left ventricular hypertrophy had a significantly lower NLR (1.430±0.409 vs. 1.797±0.521, p=0.043) and a significantly higher MNR (0.171±0.031 vs. 0.144±0.037, p=0.042). ROC curve analysis showed good diagnostic profiles for MPV (AUC: 0.729, p=0.014), NLR (AUC: 0.697, p=0.040), and MNR (AUC: 0.701, p=0.025) as predictors of LVH. In multivariate analysis, the only significant predictive factor for left ventricular hypertrophy was MNR (OR: 1.329, 95CI: 1.007-1.756).

In the third original study, it was shown that patients with PH compared to CG had higher indices of blood pressure variability: 24h ABPM SBP SD (13.7±2.5 vs. 12.6±1.8, p=0.036), 24h ABPM MAP SD (11.4±2.6 vs. 10.0±1.9, p=0.009), 24h RPI (10352±1584 vs. 8466±1203, p<0.001), 24h WSBPV (11.4±1.8 vs. 10.3±1.8, p=0.009), 24h WDBV (9.6±1.7 vs. 8.7±1.8, p=0.033), 24h WMAPV (9.2±1.6 vs. 8.0±1.7, p=0.002) and 24h CoVSBP (10.2±1.9 vs. 11.1±1.6, p=0.012). In a multivariate analysis, in the group of children with PH, MNR was a significant predictor of 24h ABPM MAP SD (β=0.290, p=0.030), 24h RPI (β=−0.348, p=0.005) and 24h WDBPV (β=0.286, p=0.028); monocyte count was the predictor of 24h RPI (β= 0.281, p=0.023), and hsCRP was the predictor of 24h WDBV (β= 0.310, p=0.018). ROC analysis showed that lymphocyte count was a significant prognostic factor for the disturbed

circadian blood pressure profile in children with PH (AUC: 0.656, p=0.037, cut-off point: 2.59 [$\times 10^3/\mu L$]).

Conclusions:

1. Patients with primary hypertension have elevated markers of subclinical inflammation compared to healthy children.
2. Pediatric patients with white coat hypertension have comparable severity of inflammation compared to patients with primary hypertension.
3. Elevated concentrations of hsCRP, adhesion molecules (ICAM-1, VCAM-1), and elevated complete blood count-derived markers: increased neutrophil, monocyte, platelet counts, and elevated indices: neutrophil-to-lymphocyte and monocyte-to-lymphocyte ratios, may be considered as immunological markers of primary hypertension in children.
4. In children with primary hypertension, there is a positive relationship between the left ventricular mass, the risk of left ventricular hypertrophy, and the severity of inflammation.
5. Monocyte-to-neutrophil ratio (MNR) may be a marker of left ventricular hypertrophy in children with primary hypertension.
6. In children with primary hypertension, there is a positive relationship between blood pressure variability and inflammation parameters – increased monocyte-to-neutrophil ratio (MNR) may be a marker of increased blood pressure variability, and an increased number of lymphocytes may be a marker of a disturbed circadian blood pressure profile.