The Diagnostic Value of Extremely Elevated Erythrocyte Sedimentation Rate in A Tertiary Pediatric Hospital

Üçüncü Basamak Bir Çocuk Hastanesinde Belirgin Yüksek Eritrosit Sedimantasyon Hızının Tanısal Değeri

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ABSTRACT

Objective: The aim of this study was to evaluate the frequency, demographic and clinical characteristics of pediatric patients with extremely elevated erythrocyte sedimentation rate (ESR) in a reference children's hospital, and to improve clinicians' ability to use extremely elevated ESR in the differential diagnosis.

Material and Methods: A retrospective cohort study was conducted to examine the clinical data of pediatric patients with extremely elevated ESR (≥100 mm/h). The patients were divided into 6 main groups according to their diagnosis as infectious, non-infectious inflammatory disease (NIID), malignancy, nephrologic, miscellaneus and unknown. Then, the specific sub-diagnoses of the patients were determined and evaluated. Clinical and laboratory data of the patients were recorded.

Results: We analyzed the results of a total of 3166 patients with high ESR (≥20 mm/h) and 189 (5.96%) patients with extremely elevated ESR were included in the final analysis. The most common etiology of extremely elevated ESR was NIID (35.9%), followed by infections (33.3%), malignancies (19.0%) nephrologic (2.6%), miscellaneus (4.7%) and unknown (4.2%). The most common specific diagnosis was acute rheumatic fever, Kawasaki disease, lymphadenitis and leukemia. The high ESR was only negatively correlated with hemoglobin and albumin levels.

Conclusion: Identifying the most common diseases that cause extreme ESR elevation in children can help clinicians in the differential diagnosis of diseases but it cannot be used as a screening tool for diseases.

Key Words: Acute phase reactants, Children, Differential diagnosis, Erythrocyte sedimentation rate

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ÖZ

Amaç: Bu çalışmanın amacı, referans bir çocuk hastanesinde belirgin olarak artmış eritrosit sedimantasyon hızı (ESR) olan pediatrik hastaların sıklığını, demografik ve klinik özelliklerini değerlendirmek ve klinisyenlerin aşırı yüksek ESR'yi ayırıcı tanıda kullanma becerilerini geliştirmektir.

Gereç ve Yöntemler: Retrospektif, kesitsel olarak planlanmış olan bu çalışmada ESR değeri ≥100 mm/saat olan pediyatrik hastalar değerlendirilmiştir. Hastalar tanılarına göre enfeksiyöz, enfeksiyöz olmayan inflamatuar hastalıklar (NIID), malignite, nefrolojik, diğer ve bilinmeyen olarak 6 ana gruba ayrıldı. Daha sonra hastaların spesifik alt tanıları belirlenerek, klinik ve laboratuvar verileri değerlendirildi.

Bulgular: Yüksek ESR'si (≥20 mm/saat) olan toplam 3166 hasta içerisinde belirgin yüksek ESR'si olan 189 (%5.96) hasta çalışmaya dahil edildi. Belirgin yüksek ESR'nin en yaygın nedeni NIID (%35.9) iken, bunu enfeksiyonlar (%33.3), maligniteler (%19.0), nefrolojik (%2.6), diğer (%4.7) ve bilinmeyen (%4.2) olarak bulundu. En sık görülen spesifik alt tanı akut romatizmal ateş, Kawasaki hastalığı, lenfadenit ve lösemiydi. Yüksek ESR, yalnızca hemoglobin ve albümin seviyeleri ile negatif korelasyon gösterdi.

Sonuç: Çalışmamız 3. Basamak, referans bir çocuk hastanesinde yapılmış literatürdeki en geniş seridir. Çocuklarda belirgin ESR yükselmesine neden olan en yaygın hastalıkların bilinmesi, klinisyenlere ayırıcı tanıda yardımcı olacaktır.

Anahtar Sözcükler: Akut faz reaktanlar, Çocuklar, Ayırıcı tanı, Eritrosit sedimentasyon hızı

INTRODUCTION

Erythrocyte sedimentation rate (ESR) indicates the fall velocity of suspended erythrocytes in plasma in a vertical tube within 1 hour in millimeters (mm). It is expressed in mm/hour. It is an easily accessible and inexpensive acute phase reactant (APR) that is frequently used in daily practice. ESR is an indirect APR, reflects plasma viscosity and the presence of the acute phase proteins, (fibrinogen, immunoglobulins, coagulation proteins, etc) that increase in inflammation reduce the electrostatic forces between red blood cells. This causes rapid aggregation and settle of erythrocytes (1,2).

Erythrocyte sedimentation rate increases in inflamation such as infections, malignancy, inflammatory diseases, renal diseases and tissue ischemia/trauma. In addition, it is known to be affected by obesity, anemia, age, gender and race (3-5). An increased ESR does not indicate a specific disease and is often used as a screening tool. However, extremely elevated ESR's (ESR ≥100 mm/h) relation with particular diseases has been discussed in many studies and its relationship with disease severity has been emphasized (6-10). Indeed, it seems that extremely elevated ESR is more frequent in some diseases.

In this study, it is aimed to evaluate the frequency, demographic and clinical characteristics of children with extremely elevated ESR. In addition, it is planned to determine the diseases that clinicians should consider in the differential diagnosis of patients with extremely elevated ESR.

MATERIALS and METHODS

This retrospective observational study was conducted in Ankara Children's Hematology Oncology Training and Research Hospital, which is a tertiary, reference pediatric hospital in Turkey. Children between the ages of 3 months and 18 years who admitted to our clinic between June 2018 and June 2019 and were found to have ESR ≥100 mm/h were included in the study. Clinical and laboratory data of the patients were recorded. Age, gender, leukocyte (WBC), hemoglobin (Hgb), platelet, absolute neutrophil counts (ANC), absolute lymphocytes counts (ALC), mean corpuscular volume (MCV), mean platelet volume (MPV), albumin, globulin, C-reactive protein (CRP) and fibrinogen levels were evaluated. ESR and other laboratory data obtained at hospital admission were included in the study. However, recurrent ESR elevations were not included in the study. Only one extremely elevated ESR value of each case was evaluated. Only 1 ESR value of each case was included in the study, recurrent extremely ESR elevations were not included.

Patient records were evaluated separately by 2 independent clinicians (CK and EKK). If there was no consensus on the definitive diagnosis of the patients, it was decided by agreement. Undiagnosed cases were evaluated as unknown. In patients with multiple diagnoses, the diagnosis of the patient was accepted as the main reason for increasing ESR. The patients were divided into 6 main groups as infectious, non-infectious inflammatory disease (NIID), malignancy, nephrologic, miscellaneus and unknown. Then, the specific sub-diagnoses of the patients in these groups were identified and evaluated.

ESR measurements were performed using the standard Westergren method. Normal ESR level was defined as <20 mm/h. ≥100 mm/h was defined as extremely elevated ESR.

Approval for this study was obtained from the Ankara City Hospital No. 2 Clinical Research Ethics Committee (E2-21-1041/24.11.2021).

Statistical analyses were performed using the SPSS 20 package programe. Results of descriptive analyses were reported as minumum (min), maximum (max) and means ± standart deviation (X±SD) for continuous variables and as number (n) and percentage (%) for categorical variables. To assess the associations between extreme ESR elevations and diseases, were performed using Mann Whitney U Test. Associations

between continous variables such as ESR, CRP were assessed using the Pearson correlation coefficient test. Diferences were regarded as statistically significant at p <0.05.

RESULTS

Totaly, 189 (5.96%) patients with extremely elevated ESR among 3166 patients with elevated ESR (>20 mm/h) were included in the final analysis. ESR ranged between 100-143 mm/h and the mean ESR level was found to be 110±10.4 mm/h.

The ages of the patients ranged from 3 months to 17.4 years and the mean was 98.0±58.8 months, and 83 of the cases were female (43.9%) and 106 were male (56.1%). No significant difference was found in terms of ESR values according to age and gender (p >0.05).

Non-infectious inflammatory disease (n=68, 36.0%) and infections (n=63 33.3%) were the most common disease group causing extremely elevated ESR. Malignancy was detected in 36 patients (19.5%), renal disease in 5 (2.6%), and miscellaneus diseases in 9 (4.76%), but the diagnosis could not be determined in 8 (4.2%) (unknown) cases (Table I). When these diagnostic groups were compared with the mean ESR levels, a significant difference was found only in the malignancy group and NIID groups (p=0.013). The differences between the mean ESR levels of the other groups were not significant.

When the definitive diagnosis of the patients were evaluated, the most common diagnoses were found to be acute rheumatic fever (ARF) and Kawasaki disease in the NIID group, lymphadenitis and acute pyelonephritis in the infectious group, and leukemia and lymphoma in the malignancy group. The associations between extremely elevated ESR and disease sub-categories are given in Table II.

Table I: Associations between extremely elevated erythrocyte sedimentation rate elevations and disease category.

Disease Category	n (%)	ESR, mm/h Mean±SD
NIID	68 (35.98)	106±10.6
Infections	63 (33.33)	111±9.5
Malignancy	36 (19.05)	113±10.4
Miscellaneus	9 (4.76)	116±13.8
Unknown	8 (4.23)	108±10.4
Nephrologic	5 (2.65)	112±9.3
Total	189 (100)	110±10.4

ESR: *Erythrocyte sedimentation rate,* ***NIID:*** *Non-Infectious İnflamatory Diseases*

Table II: Associations between extremely elevated erythrocyte sedimentation rate elevations and diseases in study group.

Disease Category/ Disease Sub-category	Patients n (%)
Non-Infectious İnflamatory Diseases	
Acute Rheumatic Fever	26 (13.8)
Kawasaki Disease	20 (10.6)
Juvenile İdiopathic Arthritis	9 (4.8)
Familial Mediterranean Fever	4 (2.1)
Systemic Lupus Erythematosus	3 (1.6)
Reactive Arthritis	2 (1.1)
Periodic Fever Syndrome	2 (1.1)
Henoch-Schoenlein Purpura	1 (0.5)
Ulcerative Colitis	1 (0.5)
Infections	
Lymphadenitis	14 (7.4)
Acute Pyelonephritis	9 (4.8)
Bacteremia-Sepsis	8 (4.2)
Pneumonia	8 (4.2)
Septic Arthritis	6 (3.2)
Soft Tissue İnfections	5 (2.6)
Acute Gastroenteritis	4 (2.1)
Osteomyelitis	2 (1.1)
Deep Neck İnfections	2 (1.1)
Tuberculosis	1 (0.5)
Intracranial Abscess	1 (0.5)
İntra-Abdominal Abscess	1 (0.5)
Pericarditis	1 (0.5)
Cat Scratch Disease	1 (0.5)
Malignancy	
Leukemia	12 (6.3)
Lymphoma	8 (4.2)
Ewing Sarcoma	3 (1.6)
Neuroblastoma	3 (1.6)
Osteosarcoma	2 (1.1)
Rhabdomyosarcoma	2 (1.1)
Hepatoblastoma	1 (0.5)
Medulloblastoma	1 (0.5)
Pancreatic Carcinoma	1 (0.5)
Intestinal Carcinoma	1 (0.5)
HLH	1 (0.5)
Nephrologic	
Chronic Renal Failure	2 (1.1)
Nephrotic Syndrome	2 (1.1)
Acute Glomerulonephritis	1 (0.5)
Miscellaneus	
Aplastic Anemia	6 (3.2)
GIS Bleeding	1 (0.5)
ITP	1 (0.5)
PTE	1 (0.5)

HLH: *Hemophagocytic lymphohistiocytosis,* ***GIS:*** *Gastrointestinal system,* ***ITP:*** *Idiopathic thrombocytopenic purpura,* ***PTE:*** *Pulmonary Thromboembolism*

In the correlation analyses there was only moderately negative correlation between ESR and hemoglobin (r:-0.46) levels and weakly negative correlation between ESR and albumin levels (r:-0.21). There was no correlation with ESR and the other laboratory parameters. The correlation analysis is given in Table III.

Table III: Corelation analyses of ESR with the other laboratory parameters in study group.

Laboratory Parameters	n	Mean±Std. Deviation	Corelation coefficient value (r)
Leukocyte, 10^3/µL	185	12532.9±9790.6	NA
HGB, g/dL	185	9.7±1.6	-0.46
MCV, fL	185	78.6±7.2	NA
Platelets, 10^3/µL	185	398870.2±263792.9	NA
MPV, fL	183	7.4±1.0	NA
ANC, %	172	8159.3±7894.4	NA
ALC, %	172	3006.4±4265.4	NA
Albumin, g/dL	149	3.5±0.5	-0.21
Globulin, g/dL	149	3.6±0.9	NA
CRP, mg/dL	189	12.1±10.0	NA
Fibrinogen, mg/dL	21	587.7±128.8	NA

NA: *No Association,* ***HGB:*** *Hemoglobin,* ***MCV:*** *Mean Corpuscular Volume,* ***MPV:*** *Mean Platelet Volume,* ***ANC:*** *Absolute Neutrophil Count,* ***ALC:*** *Absolute Lymphocyte Count,* ***CRP:*** *C-Reactive Protein*

DISCUSSION

To the best of our knowledge this is the largest study in children with extremely elevated ESR. In this study, extremely elevated in ESR was found in approximately 6% of all children with elevated ESR. In addition, about 96% of the children with extremely elevated ESR were diagnosed with various diseases. This suggests that extremely elevated ESR in children is associated with explainable and diagnosable diseases.

In our study, extremely elevated ESR was found most frequently in NIID. However, many studies have shown that infections are the most common group of diseases that increase ESR excessively. Schimmelpfennig et al. (11) found infectious diseases as 55%, connective tissue diseases or renal diseases as 25% in 156 children with extremely elevated ESR. Abbag et al. (12) evaluated 99 children and reported that the most common cause was infection (49.5%), followed by NIID (26.3%), malignancy (12.1%), and renal diseases (8.1%) . Aydoğan et al.(13) reported 66 pediatric patients in a tertiary pediatric hospital in Ankara and found infectious diseases as 54.5%, rheumatic diseases as 16.7% and renal diseases as 12.1%. Similarly, Özkan et al. (14) detected infectious diseases in 48% and rheumatological diseases in 18% of 182 children.

The most common infectious diseases in our study were lymphadenitis, acute pyelonephritis, bacteremia-sepsis and pneumonia. In the literature, pneumonia, soft tissue infections, bacteremia and meningitis were pointed out as the most common infectious diseases that cause extreme elevation in ESR (11-16). Most of these diseases are vaccine-preventable diseases. It is known that the frequency of infectious diseases such as pneumonia and meningitis has decreased in our country with the increasing vaccination rates and the new vaccines added to the vaccination schedule. Contrary to the other studies, the frequency of NIID in our study was higher than that of infectious diseases. This can be explained by the fact that our study was conducted in a single center and with a limited number of patients. In addition, we think that 8 undiagnosed patients may be associated with a possible infection. Nevertheless, NIID was higher in our study compared to similar studies in the literature. In recent years, the genetic and immunological mechanisms of NIID diseases are better known, which has increased the diagnosis of these diseases. In our study, ARF and Kawasaki disease were found to be the most common NIIDs. These two diseases constituted a quarter of the entire study group. It is known that APRs are almost always elevated in patients with ARF, typical elevations in ESR (≥60 mm/h) and CRP (≥30 mg/L) are common (17). Systemic inflammation is a characteristic of Kawasaki disease, and typically elevated ESR, high CRP, thrombocytosis, leukocytosis can occur. And also elevated AFR levels are linked with disease severity and prognosis. Intravenous immune globulin (IVIG) used in the treatment of Kawasaki disease usually elevates ESR. Therefore, follow-up of patients with ESR is not appropriate after receiving IVIG (18). In our study, all extremely elevated ESR levels are recorded before IVIG treatment.

Leukemia and lymphoma were found to be the most common malignancies that cause extreme elevation in ESR in our study. It is not surprising that leukemia and lymphoma are the most common malignancies in childhood. It was found that chronic renal failure and nephrotic syndrome cause extremely elevated ESR in our study. In similar studies, it was found that the frequency of malignancy and nephrological disease in adults is higher than in children (15, 19).

Aplastic anemia was found to be the most common cause in the miscellaneous group. Anemia is known to elevate ESR because settle of erythrocytes is prevented by negative forces between erythrocytes. Therefore, ESR increases in anemia.

Among 8 patients who could not be diagnosed, 3 patients had arthralgia, 2 patients had hepatosplenomegaly, 1 patient had erythema nodosum, 1 patient had elevated transaminases, and 1 patient had high fever. The elevation in ESR in unknown group may possibly be related to an unidentified infection.

In the comparison analysis, the difference between ESR levels in the malignancy group and the NIID group was found to be significant ($p<0.05$). The difference between the mean ESR levels of the other groups was not statistically significant. The correlation analysis conducted with elevated ESR and the other laboratory parameters, only negative correlation was found with hemoglobin and albumin levels. Albumin is known as a negative APR that decreases in inflammation, which is also expected to be low in our study group (20). Parameters such as WBC, platelets, globulin, CRP and fibrinogen increase in inflammation. In our study, these values were found to be

increased. However, the lack of correlation with ESR and the other laboratory markers suggests that they may have limited benefits in the evaluation of patients with extremely elevated ESR. In addition, the relationship between extremely elevated ESR and CRP was evaluated in a limited number of studies and found no relationship between them (7,15).

Our study has several limitations, first of all, it was designed as a retrospective, single-center study. In addition, patients with ESR ≥100 mm/hr were included in the study group, and our results only reflected patients with an extremely elevated ESR. Finally, some APRs such as serum amyloid A and procalcitonin were not included in the study because of missing data.

In conclusion, extreme elevation in ESR can occur in the pediatric age group and is often related to NIID and infections. Especially ARF, Kawasaki disease, lymphadenitis and leukemia should be considered in children with ESR ≥100 mm/h. If extremely ESR elevation is detected in children, it may help in the diagnosis of some diseases in daily pediatric practice.

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