Extreme elevation of the erythrocyte sedimentation rate in children

Fuad Idrees Abbag, Jobran Maree Al Qahtani

From the Department of Child Health, College of Medicine, King Khalid University, Abha, Saudi Arabia

Correspondence and reprint requests: Fuad Abbag, FRCP(C) Professor, Department of Child Health, College of Medicine, King Khalid University P.O. Box 641, Abha, Saudi Arabia T: 0505746575 F: 072247570 fuadabbag@yahoo.com Accepted for publication January 2007

Ann Saudi Med 2007; 27(3): 175-178

BACKGROUND: Extreme elevation the of erythrocyte sedimentation rate ($ESR \geq 100$ mm/hour) is usually associated with significant diseases. This study was performed to assess its significance in pediatric patients seen in Aseer Central Hospital.

METHODS: All ESRs performed for children between September 2001 and December 2002 were reviewed. The medical records of those with an $ESR \geq 100$ mm/hr (group 1) were reviewed for age, sex, diagnosis, ESR value, hemoglobin (Hgb) value and leukocyte counts. The diagnoses were divided into seven categories: malignancy, connective tissue diseases (CTDs), tropical infections, mild infections, severe infections, renal diseases and miscellaneous. One hundred forty-five patients with an $ESR < 100$ mm/hr (group 2) were randomly selected for comparison.

RESULTS: Of 2540 ESRs, 99 were ≥ 100 mm/hr (3.9%). There were 54 males and 45 females and the mean age was 72 ± 48.2 months. Infection was the most common cause (49.5%), followed by CTDs (26.3%), malignancy (12.1%) and renal diseases (8.1%). Malignancy was associated with the lowest Hgb value (8.2 g/dL). A comparison between group 1 and group 2 considering each diagnostic category separately showed that group 1 patients with mild infections had significantly higher mean leukocyte counts and that group 1 patients with CTDs had significantly lower Hgb values than group 2 patients with the same diagnoses, but there were no significant differences between the other diagnostic categories.

CONCLUSION: The most common cause of extreme elevation of ESR is infection. This extreme elevation may be used as a sickness index, but not as a screening tool for any disease.

The erythrocyte sedimentation rate (ESR) is one of the oldest commonly used laboratory investigations. It is simple, inexpensive and useful, and its elevation is commonly used as an indicator of certain underlying diseases such as infections, inflammations and malignancies, and to monitor the progress and response to therapy. ESR refers to the rate of fall of red blood cells (RBCs) suspended in plasma. It depends upon the difference in specific gravity between RBCs and plasma, but it is influenced greatly by the extent to which the RBCs form rouleaux, which sediment rapidly. Rouleaux formation and RBC clumping are greatly enhanced by acute-phase reactants in plasma, e.g. fibrinogen, haptoglobin, ceruloplasmin, α_1 acid-glycoprotein, and C-reactive protein. It is also increased by immunoglobulins, but is decreased by albumin. RBC intrinsic factors may affect sedimentation; for example, sickle cells and spherocytes sediment slowly, while large RBCs (macrocytes) sediment rapidly. Hyperviscosity, polycythemia and extreme leukocytosis decrease sedi-

mentation while anemia (unopposed by RBC abnormality) enhances sedimentation. Therefore, high ESR is found in conditions that elevate fibrinogen level such as infections, inflammatory diseases, collagen vascular diseases, malignancies (particularly if there is tissue degeneration or metastases), end-stage renal diseases and pregnancy. Hypoalbuminemia (e.g. associated with nephrotic syndrome) elevates the ESR. It is also elevated in conditions that cause immunoglobulinemia, e.g. multiple myeloma. Extreme elevation of ESR (defined as a rate ≥ 100 mm/hour) is often associated with serious diseases.^{1,2} This study was performed to address the frequency of extreme elevation of ESR and to ascertain the causes of this extreme elevation in pediatric patients seen at Aseer Central Hospital.

METHODS

Laboratory records of ESR of children up to 13 years of age, performed in Aseer Central Hospital between September 2001 and December 2002, were reviewed.

The medical records of those children whose ESR was ≥ 100 mm/hr were reviewed and the following variables were obtained: age, sex, diagnosis, ESR value, hemoglobin value (Hgb), and leukocyte (WBC) count.

The patients were divided into seven diagnostic categories: malignancy, connective tissue diseases, tropical infections, mild infections, severe infections, renal diseases and miscellaneous diseases. Infection was considered severe if it was invasive, e.g., septicemia, meningitis, osteomyelitis, septic arthritis, lobar pneumonia, extensive bilateral bacterial bronchopneumonia and pyelonephritis; also, infections associated with hemodynamic instability were considered severe. Statistical analysis was performed using one-way analysis of variance. To make a comparison between patients with $\text{ESR} \geq 100$ mm/hr (group 1) and those with $\text{ESR} < 100$ mm/hr within the same diagnostic categories, a group of 145 patients with $\text{ESR} < 100$ mm/hr (group 2) were randomly selected and divided into the same diagnostic categories and the same variables (age, sex, Hgb value and WBC count) were obtained for the analysis. The ESR was performed using a modified Westergren technique using EDTA anticoagulated whole blood. Readings were taken after one-hour incubation.

RESULTS

During the study period, 2540 children had their ESR measured; 99 (3.9%) of them had an ESR of ≥ 100 mm/hr. There were no statistically significant differences between group 1 and group 2 in sex, age or WBC count (Table 1). The mean Hgb value in group 1 was lower than that in group 2; although this difference was statistically significant, it is of little significance clinically. The mean ESR in those with extreme elevation (group 1) was 118 ± 13 mm/hour (the highest reading was 150 mm/hour); the mean ESR in group 2 ($\text{ESR} < 100$ mm/hour) was 30.6 ± 24 mm/hour. The most common cause of extremely high ESR was infection, found in 49 patients (49.5%). The most common infec-

tions were lung infections (pneumonia, bronchiectasis and empyema), occurring in 12 patients, followed by meningitis and septic arthritis in 7 patients each; osteomyelitis in 6 patients; malaria in 5 patients; mild viral infections in 4; visceral leishmaniasis in 2 and brucellosis in 1. Connective tissue diseases were the second most common cause of extremely high ESR, found in 26 patients (26.3%). The most common of the connective tissue diseases in this series was acute rheumatic fever, encountered in 19 patients, followed by juvenile rheumatoid arthritis and Kawasaki disease in 2 patients each. Systemic lupus erythematosus occurred in 1 patient only. The third leading cause of extremely high ESR was malignancy, which occurred in 12 patients (12.1%) and included leukemias in 8 patients and lymphoma and neuroblastoma in 2 patients each. The fourth cause of extremely high ESR was renal diseases, occurring in 8 patients (8.1%) and including post-streptococcal glomerulonephritis and nephrotic syndrome in 3 patients each and uremia in 2 patients.

A comparison between the diagnostic categories in patients with $\text{ESR} \geq 100$ mm/hour (group 1) showed that the mean Hgb value in patients with malignancy was 8.2 ± 3.5 g/dL, which is significantly lower than the mean Hgb value in the other categories ($P=0.034$). Among patients with infections, those with tropical infections (malaria and leishmaniasis) had a mean Hgb value 8.6 ± 1.9 g/dL, which is significantly lower than in those with other infections. There was no significant difference in the mean WBC count between the various diagnostic groups. Table 2 shows the number and percentage of patients in the various diagnostic categories. Group 1 patients with mild infections had a significantly higher mean WBC count than group 2 patients with mild infections (Table 3). Group 1 patients with connective tissue diseases had a significantly lower mean Hgb value than group 2 patients with connective tissue diseases (Table 3). There were no other significant differences between the two

Table 1. Sex, age, WBC and Hgb values in patients with and without extremely elevated ESR.

	Sex No. (%)	Age in months (Mean $\pm$ SD)	WBC count ($\times 10^9$ /L) (Mean $\pm$ SD)	Hgb in g/dL (Mean $\pm$ SD)
Group 1 ($\text{ESR} \geq 100$) (n=99)	Male 54 (54.5) Female 45 (45.5)	72 $\pm$ 48	12.37 $\pm$ 7.1	9.66 $\pm$ 2.29
Group 2 ($\text{ESR} < 100$) (n=145)	Male 85 (58.6) Female 60 (41.4)	64.5 $\pm$ 47	10.93 $\pm$ 8.6	11.03 $\pm$ 2.26
Statistical significance	$\chi^2=0.398$ NS	t=1.213 NS	t=1.376 NS	t=4.625 Significant

NS=Not statistically significant

Table 2. Disease categories in patients with and without extremely elevated ESR.

	Malignancy No. of patients (%)	Connective tissue diseases No. of patients (%)	Severe infections No. of patients (%)	Mild infections No. of patients (%)	Tropical infections No. of patients (%)	Renal diseases No. of patients (%)	Miscellaneous No. of patients (%)
Group 1 ESR ≥100mm/hr. (n=99)	12 (12.1)	26 (26.3)	31 (31.3)	10 (10.1)	8 (8.1)	8 (8.1)	4 (4)
Group 2 ESR<100mm/hr. (n=145)	10 (6.9)	15 (10.3)	11 (7.6)	64 (44.1)	7 (4.8)	18 (12.4)	20 (13.8)
Statistical significance	$\chi^2=1.958$ NS	$\chi^2=10.663$ Significant	$\chi^2=23.242$ Significant	$\chi^2=32.256$ Significant	$\chi^2=1.079$ NS	$\chi^2=1.160$ NS	$\chi^2=6.309$ NS

NS=Not statistically significant

Table 3. Age, white blood cell (WBC) count and hemoglobin levels in patients with and without extremely elevated ESR within the same diagnostic categories.

	Diagnostic categories					
	Malignancy	Connective tissue diseases	Severe infection	Mild Infection	Tropical infection	Renal diseases
	Group 1 (n=12)	Group 1 (n=26)	Group 1 (n=31)	Group 1 (n=10)	Group 1 (n=8)	Group 1 (n=8)
	Group 2 (n=10)	Group 2 (n=15)	Group 2 (n=11)	Group 2 (n=64)	Group 2 (n=7)	Group 2 (n=18)
Age (months)						
Group 1 ESR ≥100	92.8±60	93.2±37.9	55.6±47.3	68.1±49.5	59.6±47	62.4±42.2
Group 2 ESR <100	65.8±43.3	88.6±36.8	29.3±20.5	54.6±46.7	70.1±43.6	100.8±48
Significance	t=1.191 (NS)	t=0.378 (NS)	t=1.775 (NS)	t=0.844 (NS)	t=0.446 (NS)	t=1.948 (NS)
WBC count (x10⁹/L)						
Group 1 ESR ≥100	14.2±20	9.6±3.7	14.1±6.7	15.4±5.4	9.1±6.6	13.6±5.4
Group 2 ESR <100	12.5±18.2	11.4±5.97	12.3±5.4	10.7±5.3	5.9±2.3	11.4±6.1
Significance	t=0.207 (NS)	t=1.195 (NS)	t=0.801 (NS)	t=2.602 (Significant)	t=1.405 (NS)	t=0.877 (NS)
Hemoglobin (g/dL)						
Group 1 ESR ≥100	8.2±3.5	9.6±2.7	10.4±1.6	10.6±1.5	8.6±1.9	8.7±1.9
Group 2 ESR <100	9.5±2.6	11.1±1.2	10.9±2.48	11.5±1.79	9.5±2.13	10.4±2.6
Significance	t=0.971 (NS)	t=2.031 (Significant)	t=0.766 (NS)	t=1.507 (NS)	t=0.865 (NS)	t=1.655 (NS)

NS = not statistically significant

groups.

DISCUSSION

Extreme elevation of ESR (≥ 100 mm/hour) in children is alarming and should be considered a sign of a significant underlying disease. The frequency of this extreme elevation in our pediatric patient population (3.9%) was comparable to that reported previously in other pediatric series (4.9%),² and adult series (2.5%,¹ 3%,³ 4.2%⁴), but lower than that reported from tropical areas (12%⁵). Infection was the most common cause of extreme elevation of ESR, accounting for 51% of the cases, which is similar to the findings in other pediatric series (55.8%²), and adult series (33%⁴, 44.2%¹, 45.5%⁵). Infection is the leading cause both in series from tropical regions^{1,5,6} and from non-tropical regions.^{3,4} The most common infection was pulmonary infections, accounting for 24% of all infections in this study, which is similar to the findings in other studies.^{2,4-6} The second most common infection was meningitis, accounting for 14% of infections. Although malaria, leishmaniasis and brucellosis are common in our region, they accounted only for five, two and one of the patients with ESR ≥ 100 mm/hour, respectively. Reports from tropical areas^{1,5,6} suggest that these common infections are not among the common causes of extreme elevation of ESR. Pulmonary tuberculosis, which is one of the most common causes of pneumonia associated with this extreme elevation in some tropical areas where HIV infection is common,⁶ was not encountered in the present study. Connective tissue diseases were the second most common diagnostic category causing extreme elevation of ESR, and rheumatic fever was the most common disease among this category; this is similar to the findings of other studies reporting on children² and adults.¹ In areas where both rheumatic fever and brucella arthritis

are common, an ESR ≥ 100 mm/hour may favor the diagnosis of rheumatic fever arthritis; this is particularly helpful in patients presenting with arthritis as a sole major feature. Malignancy was the third most common cause of ESR ≥ 100 mm/hour. Although malignancy was reported to be the most common cause in a very early study (58% of cases),⁷ subsequent studies have shown this to be the third leading cause.^{1,2,4} The present study is in concert with the latter finding; it also suggests that leukemia is the leading neoplastic disease causing extreme elevation of ESR in children as was shown in earlier series.² In adults, solid tumors such as bronchogenic carcinoma, hepatocellular carcinoma, gastric carcinoma are the leading neoplastic causes of ESR ≥ 100 mm/hour,¹ and this elevation is often associated with metastasis;⁴ however, ESR should not be used as a screening test for malignancy as the sensitivity of an ESR ≥ 100 mm/hour for malignancy is low, and at its best ranges from 25% to 49%.^{4,5}

Renal failure, nephrotic syndrome and glomerulonephritis are frequent causes of extreme elevation of ESR, and therefore the latter may not be a useful indicator of infections commonly encountered with these diseases (for example, peritonitis and catheter infections). Infections, malignancy, connective tissue diseases and uremia are known to increase fibrinogen level and cause anemia and these in turn may elevate the ESR. However, the mere finding of extreme elevation of ESR should not trigger lists of advanced and invasive investigations searching for some of these diseases, as the clinical scenario at hand should dictate further investigations. In conclusion, extreme elevation of ESR is uncommon in the pediatric age group and is most commonly associated with infection. Extreme elevation of ESR in children may be used as a sickness index, but not as a screening tool for diseases.

REFERENCES

1. Cheah JS, Ransome GA. Significance of very high erythrocyte sedimentation rates (100 mm or above in one hour) in 360 cases in Singapore. *J Trop Med Hyg* 1971; 74(1): 28-30.
2. Schimmelpenninck RW Jr, Chusid MJ. Illnesses Associated with Extreme Elevation of the Erythrocyte Sedimentation Rate in Children. *Clin Pediatr (Phila)* 1980; 19(3): 175-8.
3. Ford MJ, Innes JA, Parrish FM, Allan NC, Horn DB, Munro JF. The significance of gross elevations of erythrocyte sedimentation rate in a general medical unit. *Eur J of Clin Invest* 1979; 9(3): 191-4.
4. Fincher RM, Page MI. Clinical Significance of Extreme Elevation of the Erythrocyte Sedimentation Rate. *Arch Intern Med* 1986; 146(8): 1581-3.
5. Stein CM, Xavier R. Extreme elevation of the erythrocyte sedimentation rate in patients admitted to a general medical ward in Harare, Zimbabwe. *J Trop Med Hyg* 1989; 92: 259-62.
6. Levay PF, Retief JH. Causes of high erythrocyte sedimentation rates in an inpatient population. *South African Medical Journal* 2005; 95(1): 45-6.
7. Zacharski LR, Kyle RA. Significance of extreme elevation of erythrocyte sedimentation rate. *JAMA* 1967; 202(4): 264-6.