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DIAGNOSTIC VALUE OF MEAN PEROXIDASE INDEX IN EARLY KAWASAKI DISEASE

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ABSTRACT

The charts of 27 patients with Kawasaki disease (KD) admitted to Nemazee Hospital in Shiraz from January 1991 to October 1998 were reviewed to identify the results of mean peroxidase index (MPXI) values, a measure of neutrophil staining intensity, obtained by the Technicon H_1 analyzer (Technicon Instruments Corp., Tarrytown, NY) within the first 10 days of the illness; 2 separate groups of patients were assessed as control subjects: 27 disease control (DC) children with fever plus one other KD criterion; and 27 laboratory control (LC) subjects with nonfebrile disorders interpreting also as a normal reference population. Compared with control groups, patients with KD had lower quantities of MPXI [(Mean$\pm$SD, -11.71$\pm$5.87 in KD group) vs. (1.53$\pm$4.30; $p<0.001$ in DC group, and 1.74$\pm$6.52, $p<0.001$ in LC group)]. Depending on the location of the cut-off point expressed on an interval scale, this test had the ability to be 100% specific (if MPXI<-6.0) and 100% sensitive (if MPXI>0).

Considering the low prevalence of hereditary myeloperoxidase (MPO) deficiency (1 in 2000), measurement of MPXI, when performed as part of a complete count on an automated hematology instrument, could be counted as an important adjunct to clinical evaluation and also according to the low values of MPXI in patients with KD, it can be included among the acquired causes of MPO deficiency.

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Keywords: Acute phase, Mucocutaneous lymph node syndrome, Myeloperoxidase deficiency.

INTRODUCTION

Kawasaki disease (KD) is an acute vasculitis of infants and children that results in coronary artery abnormalities in 20% to 25% of patients if untreated.[1] Administration of intravenous gammaglobulin to children with acute KD within the first 10 days of illness appears to prevent or markedly reduce the overall prevalence of cardiovascular sequelae.[2] Thus it is highly desirable to identify patients with KD early in the course of their illness.

In the absence of a definitive laboratory test result, the diagnosis of KD is dependent on the assessment of clinical features that may be mimicked by other disease processes. Indeed, the differentiation of KD from other infections and immunologic disorders constitutes a major challenge for the practitioner.[3]

Upon reviewing the charts of patients with KD we noticed the low values of mean peroxidase index (MPXI), performed as part of an automated complete blood count (CBC). The purpose of our study was to determine whether measurement of MPXI could be included as a reliable adjunct to the clinical features for early diagnosis of KD.

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MATERIAL AND METHODS

KD patients

The medical records of all children with a diagnosis of KD seen at Nemazee Hospital in Shiraz from January 1991 to October 1998 were reviewed. Twenty-seven records met the following inclusion criteria and were further examined: (1) Typical KD was diagnosed by the presence of fever for 5 or more days with at least four out of five criteria.[4] (2) CBC including MPXI measurement had been performed within 10 days of the onset of fever, by a Technicon H_1 analyzer (Technicon Instruments Corp., Tarrytown, NY), and the results were enclosed in the chart. Twenty-two patients were excluded from the study. Five patients did not meet the first inclusion criterion and 17 patients did not satisfy the second one.

Disease control group

At this phase of the study we performed a retrospective chart review of 27 children who met the following inclusion criteria: (1) The patients should have a definitive diagnosis other than KD but KD was included in the list of differential diagnoses.[5] (2) Considering the age range of patients with KD, the patient's age should be within this range (from 2 weeks to 11 years).[6] (3) Patients were eligible for this study if they had fever and at least one other manifestation suggesting KD. (4) The result of automated CBC including MPXI was registered in the charts. They had a variety of diagnoses as follows: eleven patients with systemic-onset juvenile rheumatoid arthritis, six with Epstein-Barr virus infection, three with erythema multiforme, two patients with staphylococcal scalded skin syndrome, two with drug rash, one with serum sickness, one with measles, and one with scarlet fever.

Laboratory control group

To assess whether the observed values of MPXI in patients with KD could be attributed to laboratory error, we reviewed the medical records of 27 patients admitted to the same hospital after acute trauma. The patients were tested by the same H_1 instrument, and were matched by date of automated CBC analysis, so that for each case one control was selected who was definitely analogous from the view point of the date and shift of test performance. This group was also relied on as a normal reference population.

Laboratory methods

Venous blood samples for all patients in the hospital were collected in tripotassium ethylenediaminetetraacetic acid (EDTA) tubes. The Technicon Instrument identifies polymorphonuclear neutrophils (PMNs) by quantitating peroxidase activity using flow cytochemistry. In this system, PMNs deficient in myeloperoxidase (MPO) appear as "large unstained cells" in the peroxidase channel and are readily identified.[7] The MPXI (manufacturer's normal range -10 to +10), a measure of neutrophil staining intensity, enables detection of patients with congenital or acquired MPO deficiency.[7,8]

Statistical analysis

Sensitivities, specificities and likelihood ratios for consecutive levels of MPXI were calculated according to standard formula.[9,10] Student's *t*-test was used for hypothesis testing (*p* value) of the differences between results obtained in the two comparing populations. For the automated CBC assay, the cut-offs of MPXI were evaluated by using a receiver operator characteristic curve analysis.[11,12]

RESULTS

Patients with KD and disease control subjects were comparable with respect to age (mean±SD, 4.3±2.1 vs. 4.9±2.9 years, $p>0.31$) and days of illness-which was counted from the onset of fever-at the time of the automated CBC analysis (7.4±1.8 vs. 7.9±2.3 days, $p>0.38$).

All patients with KD had negative values for MPXI. Considering the MPXI measures in patients with KD there were significant differences in comparison with control groups. The results are expressed as mean±SD for descriptive purposes in Table I.

To examine the issue of a cut-off (a discriminant level for predicting KD), sensitivity, specificity and likelihood ratios were analyzed for different levels of MPXI (Table II).

Table I. MPXI values in patients with KD: comparison with control groups.

	KD group (n= 27)	DC group (n= 27)	LC group (n= 27)	*p* value: KD group vs. DC group	*p* value: KD group vs. LC group
MPXI					
Mean±SD	-11.71±5.87	1.53±4.30	1.74±6.52	<0.001	<0.001
Range	(-22.9 - -0.1)	(-5.9 - 10.8)	(-10.6 - 13.6)		

KD, Kawasaki disease; DC, disease control; LC, laboratory control; MPXI, mean peroxidase index (a measure of neutrophil staining intensity). Values are given according to H_1 manufacturer's scaling as the mean±SD.

Table II. Trade-off between sensitivity and specificity, with LR calculation in 27 patients with KD and 27 DC patients.

MPXI ≤ (cut-offs)	Sensitivity	Specificity	1-Specificity	LR+
-12	63%	100%		
-11	67%	100%		
-10	70%	100%		
-9	70%	100%		"Rule in" KD
-8	74%	100%		
-7	74%	100%		
-6	78%	100%		
-5	81%	96%	0.04	20.25
-4	81%	93%	0.07	11.57
-3	88%	88%	0.12	7.33
-2	96%	81%	0.19	5.05
-1	96%	70%	0.30	3.2
0	100%	48%	0.52	1.92
+1	100%	41%	0.59	"Rule out" KD
+2	100%	37%	0.63	

DC, Disease control; KD, Kawasaki disease; LR+, Likelihood ratio of a positive test result; MPXI, Mean peroxidase index.

The receptor operator characteristic curve for the MPXI levels is shown in Figure 1. The point marked on the left side of the curve and its numerical value (MPXI<-5) indicates the cut-off corresponding to the best accuracy (i.e. fewest false negative and false positive results for the test). Highest safety (i.e. sensitivity, 100%) is the cut-off that includes all MPXI levels in patients with confirmed KD (MPXI > 0).

It is worthy to mention that on follow up all patients of the KD group developed positive measures of MPXI up to the end of the subacute stage (i.e. approximately 3 weeks after the onset of fever).

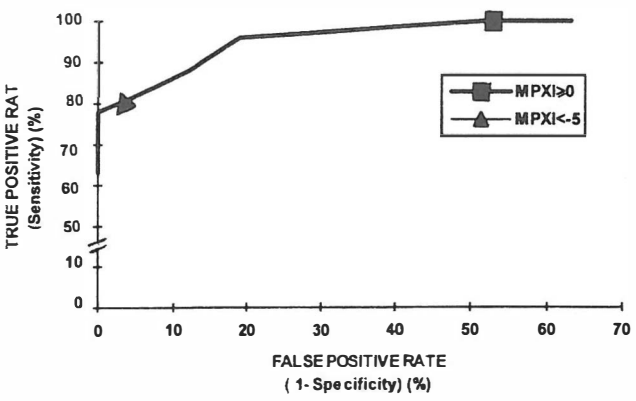

Fig. 1. Receiver operator characteristic (ROC) curve for MPXI as a diagnostic test for Kawasaki disease (see Table II for further description).

DISCUSSION

More than 125,000 cases of KD had been recognized in Japan by the end of 1994. KD has replaced acute rheumatic fever as the leading cause of acquired heart disease in children in the United States and many other areas.[1] In spite of the fact that more than three decades have elapsed since the introduction of KD,[5] up till now a diagnostic test capable of differentiating early KD from other febrile illnesses has not yet been developed, and it is diagnosed solely on clinical grounds.[8,13]

For the following reasons we conclude that clinical criteria alone are inadequate to reliably differentiate patients with KD from a comparative group: (1) The disease may have a poor prognosis if misdiagnosed and consequently left untreated; and (2) Using clinical criteria, the diagnosis of KD could be impossible in infants and in patients with atypical presentations.[2,14-16] So a diagnostic test is necessary to help differentiate KD from similar illnesses.

This study demonstrated that in the acute stage of KD we can confirm the diagnosis by using MPXI, measured by an automated CBC analyzer. In comparison to the current laboratory tests recommended in KD, MPXI has several advantages as follows:[4,17-20] (1) Considering the location of the cut-off point of MPXI, it can be 100% specific or 100% sensitive. Depending on the patient's condition, it is an arbi-

trary decision to select each level. (2) The test is simple and quick. (3) The test is very safe and noninvasive. (4) Due to its automated nature, intraobserver and interobserver disagreement is obviated.[19]

We therefore suggest this test to be requested in any patient suspicious of KD. If the MPXI has a positive value we will be able to "rule out" KD and if its value is below -6 (since the normal range of MPXI is from -10 to +10, for greater assurance the cut-off point can be considered below -10), KD can be "ruled in" (Table II). Moreover, considering the mean, range and distribution of MPXI values in patients with KD (Table I), and bearing in mind that there are a few causes of acquired MPO deficiency, as mentioned in the literature,[8,12,22] KD can be considered among the acquired disorders with associated MPO deficiency. Comparing the MPXI values in the KD group with the laboratory control group (as a normal reference population) confirms our statement (Table I).

Finally, we hope this article as a landmark effort prepares a new way for detection of the etiologic agent(s) of KD and development of a specific diagnostic test.

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