



Original Article

Laboratory Biomarkers to Facilitate Differential Diagnosis between Measles and Kawasaki Disease in a Pediatric Emergency Room: A Retrospective Study

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Abstract. This retrospective study was conducted to analyze clinical and laboratoristic parameters to individuate specific differences and facilitate differential diagnosis between Measles and Kawasaki Disease (KD) at first evaluation in an emergency room. We found similar clinical features as duration of fever and number of KD criteria ($p > 0.5$) but significant differences in white blood cell count, neutrophils, CRP and LDH levels ($p < 0.001$). LDH value ≥ 800 mg/dl had sensibility of 89% and specificity of 90% for Measles while CRP ≥ 3 mg/dl had sensibility 89% and specificity of 85% for KD. The combined use of CRP, LDH and AST showed accuracy of 86.67%.

Keywords: Measles , Kawasaki disease.

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Introduction. Measles is a highly contagious systemic viral disease that remains one of the most important causes of worldwide morbidity and mortality in children despite the availability of a safe and efficacious vaccine.¹ Ongoing measles outbreaking in Europe has caused thousands of cases among all age groups and 35 deaths in the last 12 months.²

Measles should always be considered in the approach to any child with fever and erythematous rash.³ Among these conditions, one of the most common differential diagnosis includes Kawasaki

Disease (KD), mainly because of the similar clinical features of persistent fever, no purulent conjunctivitis, and rash. Clinical differential diagnosis may be sometimes difficult, particularly with incomplete KD cases. A further difficulty is represented by the relatively low incidence of measles in developed countries thanks to vaccine introduction, so it can frequently lead to misdiagnosis. The microbiological confirmation is not always available in all settings. When possible, it may require 24 to 72 hours for results, depending on different laboratories. Because of

the difficulty of ever getting a definite differential diagnosis and the potential complication of delayed diagnosis and treatment of KD, most general practitioners and pediatricians admit doubtful cases to the emergency department (ED) of main hospitals. Similarly, primary care emergency settings often transfer suspected measles vs. KD cases to academic hospitals. This approach causes a significant increase in health costs and working impact on main emergency departments with many implications on routine activities.

For these reasons, we performed this retrospective study to analyze clinical and laboratory features of measles in comparison with KD to make an easier differential diagnosis at the first evaluation in ED.

Methods. The study was approved by the Ethics Committee of our Hospital (1452_OPBG_2017).

A retrospective single-center study was conducted. We evaluated data of all children aged between 1 month and 14 years admitted to the Emergency Department of Bambino Gesù Children between January 2016 and April 2017 because of fever lasting > 3 days and rash and having a final registered diagnosis of confirmed Measles or KD, according to international classifications.^{3,4} Data from these children were independently reviewed by three authors.

Definitions. Confirmed measles: the World Health Organization (WHO) clinical case definition of measles is a viral disease presenting as fever, generalized maculopapular rash (nonvesicular),⁵ and cough, coryza, or conjunctivitis.⁶ Koplik spots (small white spots on the buccal mucosa)⁷ are pathognomonic, but may not always be present. The measles diagnosis was considered definite in case of an acute febrile rash illness with isolation of measles virus from a clinical specimen, or detection of measles-virus specific nucleic acid using polymerase chain reaction, or IgG seroconversion or a significant rise in measles immunoglobulin G antibody, or a positive serologic test for measles immunoglobulin M antibody, or direct epidemiologic linkage to a case confirmed by one of the methods above.⁸

Kawasaki disease: The final diagnosis of KD is based on the presence of ≥ 5 days of fever and ≥ 4 of the following main clinical features: bilateral non-exudative conjunctivitis, erythema of lips and

oral mucosa, changes in the extremities, skin rash, and cervical lymphadenopathy.⁴

Incomplete KD occurs in patients presenting a typical fever without a sufficient number of primary clinical criteria, with or without coronary artery involvement. This kind of KD is frequent in children younger than 12-24 months and should be suspected in every child younger than six months affected by fever for more than seven days and a documented systemic inflammation, without any other possible cause.⁴

Inclusion criteria were: definitive measles, typical or incomplete KD.

Exclusion criteria were: age ≤ 30 days and > 18 years; the presence of congenital or acquired immunodeficiency, malignancies, metabolic disorders; children who did not undergo all clinical and laboratory evaluations in the emergency department.

Data were collected from medical records, electronic records for laboratory results, and radiology/echocardiographic results when performed. Demographic and clinical details, blood results, and clinical management including type, route, and duration of any treatments, were entered into an electronic database. Only clinical findings and primary level blood tests performed in the emergency room were evaluated for statistical analyses.

Informed consent was obtained from all families.

Statistical analysis. Statistical analysis was performed using the SPSS software (IBM SPSS Statistics, version 24.0, Chicago, IL, USA). The normality of the data distribution was assessed by the Kolmogorov–Smirnov test. Values were expressed as arithmetic means \pm standard deviation (SD) for continuous variables normally distributed, median and interquartile range (IQR) for not normally distributed data, or number and percentage (%) for categorical variable. The Mann-Whitney test, Student's t-test were used to compare non-normal and normal data respectively while the χ^2 was used to compare categorical variables. A p-value < 0.05 was considered statistically significant.

We analyzed the sensitivity and specificity of each laboratory parameter that was statistically different between the 2 study groups. For each value, we performed receiver operating characteristics curve analysis to select the optimal

value for minimizing classification errors. We have created a model with three parameters (LDH, CRP e AST) to obtain the best combination of sensitivity, specificity, and accuracy.

Results. A total of 111 children were included in the study (males 54%, mean age 16 months).

47 children were diagnosed having KD (of which four incomplete; coronary artery involvement present in 17 cases, in particular: six coronary hyperechogenicity, nine coronary enlargements, one coronary aneurysm, one mitral insufficiency) and 64 Measles (**Table 1** and **2**). Children's median age at onset of symptoms was similar between the two groups: KD: 23 months (13-36), measles: 14 months (6 – 44,5); p not significant (ns).

We found a similar mean duration of fever (KD $5,64 \pm 3,28$ vs measles $4,76 \pm 2,03$; p ns) and a similar number of KD clinical criteria on admission to our Emergency Department in the two groups (KD median 3 (1-4) vs measles median 2 (2-2); p ns). Blood tests revealed statistically significant differences in white blood cells count,

neutrophils and lymphocytes populations, hemoglobin concentration and platelet count (**Table 1**). Similarly, C-Reactive Protein (CRP) and lactic dehydrogenase (LDH) values showed significant differences: CRP was higher among the Kawasaki-group (KD mean 9,92 mg/dl; 5,8 – 14,11) than in the Measles-group (mean 0,76 mg/dl; 0,32 – 2), $p < 0,001$, while LDH presented a different trend showing higher values in the Measles-group (KD mean $626,04 \pm 228,54$ mg/dL vs measles mean $1202,81 \pm 437,82$ mg/dL, $p < 0.001$).

LDH ≥ 650 mg/dl had a sensitivity of 93% and a specificity of 78% for Measles diagnosis with an AUC (mean \pm SE) of 0.917 ± 0.33 (CI 95% 0,853–0.981; $p < 0.001$);

A CRP ≥ 3 mg/dl has a sensitivity 89% and a specificity of 85% for KD diagnosis and an AUC (mean \pm SE) of 0.937 ± 0.26 (CI 95% 0,885–0.988; $p < 0.001$).

An AST ≥ 55 UI/l has a sensitivity and specificity of 72% for measles diagnosis and an AUC (mean \pm SE) of 0.768 ± 0.052 (CI 95% 0,666–0.869; $p < 0.001$).

Table 1. Characteristics of the study population.

	Kawasaki (n° 47)	Measles (n° 64)	P value
Males, (%)	26 (55)	34 (53)	ns
Age, months	23 (13-36)	14 (6 – 44,5)	ns
Fever, days	$5,64 \pm 3,28$	$4,76 \pm 2,03$	ns
Conjunctivitis (%)	30 (66)	56 (87)	0,016
Rash (%)	34 (75)	61 (95)	0,003
Lymphadenopathy (%)	13 (29)	11 (17)	ns
Extremity changes (%)	15 (33)	0 (0)	< 0,001
Mucositis (%)	20 (44)	5 (8)	< 0,001
Kawasaki criteria	Media $2,49 \pm 1,34$ median 3 (1-4)	Media $2,08 \pm 0,67$ median 2 (2-2)	ns

Table 2. Laboratory data of the study population.

	Kawasaki	Measles	Healthy donors	Pvalue (K vs M)
White Blood Cells 10^3 /mL	$14,271 \pm 5,378$	$5,974 \pm 2,970$	8750 ± 3325	< 0,001
Neutrophils 10^3 /mL	$9,194 \pm 4,905$	$3,086 \pm 1,802$	4645 ± 3325	< 0,001
Lymphocytes 10^3 /mL	$3,435 \pm 1,987$	$2,240 \pm 2,002$	$3,760 \pm 2720$	< 0,001
Haemoglobin g/dl	$10,85 \pm 1,08$	$12,09 \pm 1,55$	$13,00 \pm 2,5$	< 0,001
Platelets 10^3 /mL	$464,893 \pm 272,050$	$191,423 \pm 75,431$	$300,000 \pm 150,000$	< 0,001
Aspartate aminotransferase UI/L	34,5 (26 - 59,5)	71,0 (52 - 95)	5 - 40	< 0,001
Alanino aminotransferase UI/L	23 (14,75 - 104,25)	31 (23 - 48)	5 - 40	ns
Lactic Dehydrogenase UI/L	$626,04 \pm 228,54$	$1202,81 \pm 437,82$	$350,00 \pm 120,00$	< 0,001
Sodium mEq/l	$136,14 \pm 2,85$	$136,84 \pm 2,78$	$140,5 \pm 4,5$	ns
C-Reactive Protein, mg/dl	9,92 (5,8 - 14,11)	0,76 (0,32 - 2)	0,00 - 0,25	< 0,001

The combined use of CRP (cut-off 3 mg/dl) and LDH (cut-off 650 mg/dl) values allowed the correct classification of 71 out of 95 participants, showing an accuracy of 75%. Adding to this model AST value (cut-off 55 UI/l) the model showed an accuracy of 86%.

Discussion. We described clinical and laboratory features of children admitted to a pediatric emergency department with fever and rash, having a possible diagnosis of measles or KD. As shown in the results table, clinical manifestations of these two diseases are often overlapping; the only significant difference was found in mucositis and changes of the extremities criteria, significantly associated with KD. Indeed, Koplik spots can be useful in defining a dubious diagnosis because pathognomonic of measles but they are not always present, also in our series they were described in about 5% of cases. Interestingly, 10% of measles cases underwent echocardiography for suspected KD and one measles child experienced intravenous immunoglobulin always doubting KD.

As far as we know, beyond the assessment of white blood cells and CRP that are notoriously high in KD according to current guidelines,⁷ correlation studies between these two diseases based on standard laboratory tests have never been performed before ours. Few studies described laboratory differences between KD and measles regarding lymphocytes subsets,⁹ cytokines and chemokines^{10,11} among measles and KD but these

findings are not useful in the clinical practice. With this study, we analyzed differences in hemogram and other laboratory data and showed high sensitivity and specificity of some blood parameters in distinguishing these two conditions already at the first evaluation in the ED. In particular, we found strong evidence in the correlation of CRP, AST and LDH levels between KD and measles giving the doctor, particularly in ED, new useful items for differential diagnosis. Actually, no previous studies describe the predicting role of LDH in KD or Measles final diagnosis. Therefore more studies on a larger number of cases should evaluate if LDH and AST might be included in KD and/or measles diagnosis flow-charts.

Conclusions. It may be extremely useful performing these diagnostic tests already in ED if any diagnostic doubt is present to better identify patients who require further investigations and specific therapies. At the same time, they could be useful to avoid inappropriate admissions and to reduce healthcare costs.

Other studies on more extensive populations (including in the analyses also other infectious causes of hepatitis such as the major viral infections)¹² may be useful to confirm our result and perspective works could validate the use of conventional laboratory tests in clinical practice for differential diagnosis of KD and measles.

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