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Identification of the best cutoff points and clinical signs specific for early recognition of macrophage activation syndrome in active systemic juvenile idiopathic arthritis

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ABSTRACT

Objectives: The purpose of our study was to detect early clinical and laboratory signs that help to discriminate macrophage activation syndrome (MAS) from active systemic juvenile idiopathic arthritis (SJIA) without MAS.

Methods: Our retrospective study was based on reviewing the medical charts of the children admitted to the rheumatology department with active SJIA and definite MAS ($n = 18$) and without MAS ($n = 40$). We evaluated the data related to SJIA and MAS at the moment of the patient's admission. If the patient had signs of MAS since admission or developed definite MAS later during this flare, he was referred to the main group. The children who did not have MAS during the flare episode and did not have MAS in the past medical history were in the control group. We calculated the cutoff points for MAS parameters, performed the analysis of sensitivity and specificity, identified the predictors, and provided the preliminary diagnostic rule through "the-number-of-criteria-present" approach.

Results: The clinical signs were relevant to MAS in SJIA: oligoarticular disease course (OR = 5.6), splenomegaly (OR = 67.6), hemorrhages (OR = 33.0), and respiratory failure (OR = 11.3). The involvement of wrist (OR = 0.2), MCP (OR = 0.1), and PIP joints (OR = 0.1) was protective against MAS development. The best cutoffs for laboratory parameters were PLT $\leq 211 \times 10^9$/l, WBC $\leq 9.9 \times 10^9$/l, AST > 59.7 U/l, LDH > 882 U/l, albumin ≤ 2.9 g/dl, ferritin > 400 μg/l, fibrinogen ≤ 1.8 g/l, and proteinuria. The laboratory variables were more precise in the discrimination of early MAS than clinical: any 3 or more laboratory criteria provided the highest specificity (1.0) and sensitivity (1.0) and OR = 2997.

Conclusions: We detected clinical and laboratory markers and created preliminary diagnostic (laboratory) guidelines for early discrimination of MAS in active SJIA.

Introduction

Macrophage activation syndrome (MAS) is a severe life-threatening hematological condition, mostly complicated by systemic juvenile idiopathic arthritis (SJIA) [1]. The diagnosis of MAS can be difficult, especially in subclinical forms and in the early stage of MAS [2,3]. The early detection of MAS can lead to appropriate therapeutic interventions and change the outcomes. There are no strict criteria with enough sensitivity and specificity that are good for early MAS detection in SJIA [4]. MAS belongs to the family of histiocytic disorders, especially close to

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; anti-IL1, anti-interleukin -1; anti-IL6, anti-interleukin-6; AST, aspartate aminotransferase; AUC, area under the curve; 95% CI, 95% confidence interval; CNS, central nervous system; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GGTT, γ-glutamintranspeptidase; Hb, hemoglobin; HLH, hemophagocytic lymphohistiocytosis; ILAR, International League of Associations for Rheumatology; IQR, interquartile range; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; MCP, metacarpophalangeal joints; Me, median; Na+, sodium; OR, odds ratio; PIP, proximal interphalangeous joints; PLT, platelets; SJIA, systemic juvenile idiopathic arthritis; TMJ, temporomandibular joints; TG, triglycerides; WBC, white blood cells.

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hemophagocytic lymphohistiocytosis (HLH), but there are some differences in the pathogenesis between HLH and MAS that lead to different therapeutic approaches [5–10]. HLH is a typical genetic disorder related to T-cell and macrophage uncontrolled expansion linked to NK-cell and cytotoxic T-cell function considered to be the result of homozygous mutations in cytolytic pathway genes [11–16]. The pathogenesis of MAS is more complex and heterogenous. Decreased NK-cell activity, repeated stimulation, and hyperactivation of Toll-like receptor (TLR-9) and cytokine disbalance are other known pathogenic mechanisms underlying the MAS pathogenesis [17–21]. Despite the fact that MAS bears a close resemblance to hemophagocytic lymphohistiocytosis (HLH), the often applied HLH criteria created for genetic disorders are not applicable to early recognition of MAS in SJIA patients [22]. The prominent inflammation with an increased number of WBC and platelets and hyperfibrinogenemia typical for SJIA required a higher threshold of these parameters for MAS detection than in HLH. Fever, one of the main symptoms in SJIA and MAS/HLH, is very frequent in both conditions, so the sensitivity of fever is low. The main difference is the pattern of fever: non-remitting fever is typical for MAS/HLH and spiking remitting fever is more relevant for SJIA [23]. Due to the high intensity of thresholds of the HLH criteria they can only determinate the advanced stage of MAS, which leads to the delay in diagnosis and late start of specific treatment, which is associated with poor outcomes. Preliminary criteria of MAS in SJIA have been proposed, but these criteria had some limitations due to the lack of several laboratory measurements [24]. Several studies showed that clinical signs usually appear later and lead to the delay of MAS diagnosis, so the laboratory markers could be more sensitive and discriminative in early MAS diagnosis [24,25].

The purpose of our study was to detect clinical and laboratory signs that help to discriminate patients with an increased risk of MAS development or early MAS in active SJIA patients.

Methods

Study design and patient selection

Our retrospective study was based on reviewing the medical charts of the children who were admitted to our rheumatology department in 2005–2013 with the onset or flare of SJIA. The diagnosis of SJIA was established on ILAR definitions [26]. We collected all available information of the whole disease course and tried predominantly to use the data about the onset of SJIA. The patients with flare were included in the present study only in cases in which the data of the disease onset were missing or insufficient. All the children were divided into 2 groups. The main group consisted of patients with active SJIA with definite MAS ($n = 18$) and controls with active SJIA without MAS ($n = 40$). If the patient had signs of MAS since admission or developed definite MAS later during this flare, he or she was referred to the main group. Only the children who did not have distinctive MAS during the flare episode and did not have MAS in the past medical history were referred to the control group—SJIA without MAS. The diagnosis of MAS was based on the criteria provided by A. Ravelli [24,27,28]. Each patient recognized with definite MAS was consistent to at least Ravelli's criteria or the HLH-2004 criteria and was reassessed by at least 3 experienced physicians (1 attending physician of the patient and at least 2 from the department staff). If there was no disagreement among the physicians and the patient was consistent to at least 1 of the 2 abovementioned criteria, the patient was included in the main group. Eight patients with probable/doubtful MAS (beyond the 58 patients remained in the study) were excluded if they fell under the criteria or disagreement between physicians was reached. The disagreement was defined if the opinion of at least one of the physicians differed from the others.

We collected the data about all the clinical and laboratory SJIA-related and MAS-related signs at the moment of the patient's admission to our clinic. The clinical signs were fever ($\geq 38^{\circ}$C), rash, active joints, hepatosplenomegaly, jaundice, lymphadenopathy, cardio-respiratory involvement (pleuritis, respiratory failure, myocarditis, and pericarditis), central nervous system dysfunction (irritability, confusion, coma, seizures, and brain MRI patterns), hemorrhage syndrome, and bleeding. The number of active joints was recorded at the moment of admission to our clinic. Oligoarticular course means the patient has less than 5 active joints, if the number of active joints was more or equal to 5, the polyarticular course was implied. Among the laboratory signs, we checked hemoglobin (Hb), white blood cells (WBC), and platelets (PLT) count; erythrocyte sedimentation rate (ESR); C-reactive protein (CRP), ferritin, total serum protein, and albumin levels; triglycerides, prothrombin, fibrinogen, sodium and alanine aminotransferase, aspartate aminotransferase, γ-glutamintranspeptidase, and lactate dehydrogenase (LDH) activities; hyperbilirubinemia; and proteinuria. All blood samples were collected after fasting. We also evaluated the demographic data. The protocol of this study was approved by the local Ethic Committee of our University.

Statistics

The descriptive statistics were reported in terms of medians and interquartile ranges (IQRs) for continuous variables and in terms of absolute frequencies and percentages for categorical variables. We used the Mann–Whitney *U*-test for the comparison of quantitative variables in 2 groups and the chi-square test for the comparison of qualitative data or the Fisher's exact test in case of expected frequencies < 5. The ability of each variable to discriminate the MAS episode from systemic arthritis flare was evaluated with sensitivity and specificity analysis, with area under receiver operating characteristic curve (AUC-ROC) analysis with 95% confidence interval (CI), and by calculating odds ratio (OR) for the detection the best cutoffs of continuous variables. The higher values of OR of variables interfere better discriminatory ability. For laboratory tests, we used AUC-ROC analysis with 95% CI. For each categorical variable the analysis of sensitivity and specificity was performed. We avoided using the known “standard” threshold (i.e., threshold reported in literature before or judged as clinically meaningful), because usually these tests better discriminate the advanced stage of MAS. We used the “best” threshold obtained through the ROC curve analysis of our data because they provide the most appropriate means between sensitivity and specificity. After selection of the most significant criteria, we tried to create the diagnostic rule based on combination of these criteria. The clinical and laboratory criteria and their combination were evaluated either separately or together. For calculation of number of possible combination, we used the “n of k” procedure. The software Statistica (release 6.0, StatSoft Corporation, Tulsa, OK), Biostat, and MedCalc were used for the data analyses. $P < 0.05$ was considered to indicate a significant difference.

Results

The main demographic data on clinical and laboratory abnormalities in both groups are in Tables 1 and 2. The age of MAS onset was 6.7 (2.3–10.2) years, the interval between SJIA onset and MAS onset was 11.3 (0.8–34.8) months, and MAS duration was 68.0 (48.0–93.0) days, ranged: 11.0–336.0 days. The relapse course was experienced by 10/18 (55.6%) patients, and 2/18 patients died (11.1%). As the suspected children with MAS had typical changes,