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ABSTRACT. ***Objective.*** To identify candidate diagnostic criteria for macrophage activation syndrome (MAS) complicating systemic juvenile idiopathic arthritis (sJIA) using international consensus formation through a Delphi questionnaire survey.

Methods. A questionnaire listing 28 clinical, laboratory, and histopathologic features of MAS elicited by literature review was sent to 505 pediatric rheumatologists worldwide. Respondents were asked to select the 10 features that they felt were most important and useful in the diagnosis of MAS, and to order the 10 selected features by assigning the number 10 to the most important, and ending with 1 as the least important.

Results. The response rate was 46% (232 physicians from 47 countries). The items selected by more than 50% of respondents were, in order of frequency, falling platelet count, hyperferritinemia, evidence of macrophage hemophagocytosis in the bone marrow, increased liver enzymes, falling leukocyte count, persistent continuous fever ≥ 38°C, falling erythrocyte sedimentation rate, hypofibrinogenemia, and hypertriglyceridemia.

Conclusion. Our process led to identification of features that were felt to be most important as candidate diagnostic criteria for MAS by a large sample of international pediatric rheumatologists. (First Release Feb 1 2011; J Rheumatol 2011;38:764–8; doi:10.3899/jrheum.100996)

Key Indexing Terms:
MACROPHAGE ACTIVATION SYNDROME HEMOPHAGOCYTIC SYNDROME
SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS
HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS DIAGNOSTIC CRITERIA

Macrophage activation syndrome (MAS) is a serious, potentially life-threatening complication of childhood rheumatic diseases, which occurs much more commonly in systemic juvenile idiopathic arthritis (sJIA)[1,2,3,4,5]. Because MAS can pursue a rapidly fatal course, prompt recognition of its clinical and laboratory features and immediate therapeutic intervention are imperative. However, diagnosis of MAS can be difficult and hard to distinguish from sepsis-like syndromes, although it may also be associated with sepsis, especially in cases of intraphagocytic pathogen infections. In addition, the recognition of subclinical forms of MAS in sJIA[6,7] underscores the importance of establishing criteria sensitive enough to distinguish MAS from routine disease flare.

Although MAS bears a close resemblance to hemophagocytic lymphohistiocytosis (HLH), HLH criteria developed primarily for genetic disorders leading to hemophagocytosis[8] are not necessarily useful in defining/identifying MAS in sJIA. The main shortcoming of HLH criteria in MAS is that certain criteria may not apply to patients with sJIA. Due to the prominent inflammatory expression of the latter disease, the occurrence of a relative decrease in white blood cell count, platelets, or fibrinogen rather than the absolute decrease required by the HLH criteria may be more relevant in making an early diagnosis. Further, the minimum threshold level for hyperferritinemia required for the diagnosis of HLH (500 μg/l) is not suitable to detect MAS. It is well known that many patients with active sJIA, in the absence of MAS, have ferritin levels above that threshold[9]. In the acute phase of MAS, the ferritin level generally peaks to more than 5000 μg/l. Thus, use of a 500 μg/l threshold may not help to discriminate MAS from a flare of sJIA.

Other HLH criteria that are not readily applicable to MAS are the demonstration of low or absent natural killer cell activity or soluble interleukin 2 (IL-2) receptor α above

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normal limits for age, as these tests are not routinely performed in pediatric rheumatology settings. We recently found that the diagnostic guidelines for HLH were highly specific in our patients with sJIA-associated MAS but lacked sensitivity[10]. Preliminary diagnostic guidelines for MAS in sJIA have been proposed[11]. However, that study has several limitations, including the lack of several laboratory measurements in a number of patients and insufficient data for some of the laboratory measures evaluated. Moreover, these criteria have yet to be validated.

In recent years, an international working group of pediatric rheumatologists with specific interest in MAS was established. One of the leading aims of the group was the development of a robust set of criteria for MAS complicating sJIA, based on expert consensus and analysis of a large sample of MAS and control patients. We present the results of the first step of the project, whose specific aim was to identify candidate items using international consensus formation through the Delphi survey technique.

MATERIALS AND METHODS

Questionnaire survey. A Delphi questionnaire[12] compiled by a clinician (AR) and a statistician (AP) and revised and approved by the members of the MAS working group was circulated by e-mail to all center directors of the Pediatric Rheumatology International Trials Organization (PRINTO) and to all members of the Pediatric Rheumatology Collaborative Study Group (PRCSG), and the Childhood Arthritis and Rheumatology Research Alliance (CARRA). Not all organizations were represented equally, as many respondents belonged to more than one of these networks. A total of 505 pediatric rheumatologists worldwide were sent the survey. A reminder e-mail was sent after 6 weeks to all investigators who had not replied to the first e-mail. A further reminder e-mail was sent 6 weeks later to all investigators who had not replied to the second e-mail.

The questionnaire listed 28 clinical, laboratory, and histopathologic features thought most likely to be helpful and relevant in the diagnosis of MAS complicating sJIA, identified through literature review (Table 1). Respondents were first asked to select the 10 features that in their opinion were most important and useful in the diagnosis of MAS in sJIA. Second, they were asked to rank-order the 10 selected features by assigning the number 10 to the most important one, and end with 1 as the least important. They were instructed to use each rank only once, even though they could feel some features were equally important (i.e., no ties were allowed). At the end of the questionnaire, respondents were asked to add any feature that was considered relevant by them and was missing from the list. Importantly, no threshold level was provided for laboratory features, as the optimal diagnostic level is meant to be calculated in the second phase of the project, through analysis of data from patients with MAS and control patients.

Statistics. Comparison of percentage frequencies among groups was performed by means of the chi-square test, or the Fisher exact test in case of expected frequencies less than 5. Bonferroni adjustment was applied as a correction for multiple comparisons to explore post-hoc differences between pairs of patient groups. All statistical tests were 2-sided; a p value < 0.05 was considered statistically significant. The statistical package used for analyses was Statistica (StatSoft Corp., Tulsa, OK, USA).

RESULTS

Of the 505 pediatric rheumatologists who were sent the Delphi questionnaire, 232 (45.9%) from 47 countries provided feedback. Ninety-two respondents practiced in Europe, 90 in North America, and 50 in other continents (28 Latin America, 16 Asia, 3 Africa, and 3 in Oceania). There was more than one participant in less than 5% of the centers.

The frequency of selection of the 28 MAS features by questionnaire respondents is shown in Table 1, including the median and mean ranks. The percentage of respondents attributing high rank to each feature is shown in the last 2 columns. The items selected by more than 50% of respondents (9 in total) were, in order of frequency: falling platelet count, hyperferritinemia, evidence of macrophage hemophagocytosis in the bone marrow, increased liver enzymes, falling leukocyte count, persistent continuous fever ≥ 38°C, falling erythrocyte sedimentation rate (ESR), hypofibrinogenemia, and hypertriglyceridemia. Similarly, the items that achieved a median rank > 5 were, in order of median, evidence of macrophage hemophagocytosis in the bone marrow, hyperferritinemia, persistent continuous fever ≥ 38°C, falling platelet count, falling ESR, increased lactic dehydrogenase, hypofibrinogenemia, and increased soluble IL-2 receptor α.

Table 2 compares the frequencies of feature selection among respondents from centers in Europe, North America, and other continents. Overall, it appeared that North American physicians ascribed less importance to clinical manifestations [namely, persistent continuous fever ≥ 38°C, central nervous system (CNS) dysfunction, hemorrhagic manifestations, and liver enlargement] than did physicians from Europe or elsewhere. Physicians from other continents less frequently selected hyperferritinemia than did physicians from Europe or North America, whereas hypertriglyceridemia was selected most frequently by European physicians. European physicians also less commonly selected falling ESR, prolongation of clotting times, and increased D-dimer than did physicians from North America or other continents. Increased liver enzymes, increased soluble IL-2 receptor α, and increased soluble CD163 were indicated more frequently by North American physicians than by physicians from Europe or other continents.

Very few of the respondents added features not included in the list, which suggests that most participants agreed that the items listed in the survey were the most important diagnostic manifestations of MAS.

DISCUSSION

Using a consensus formation process that involved a large number of pediatric rheumatologists worldwide, we determined the relative diagnostic importance of 28 clinical, laboratory, and histopathologic features of sJIA-associated MAS. Of these 28 features, the following 9 were selected by more than 50% of respondents and were most frequently given the highest ranks: falling platelet count, hyperferritinemia, evidence of macrophage hemophagocytosis in the bone marrow, increased liver enzymes, falling leukocyte count, persistent continuous fever ≥ 38°C, falling ESR,

Table 1. Frequency of selection of the 28 MAS features by the 232 questionnaire respondents. median and mean ranks of features, and percentage of respondents attributing high rank to each feature.

Feature	No. (%) Respondents Who Selected the Feature	Median Rank	Mean (SD) Rank	Respondents Giving Rank 8-10 to Feature, %	Respondents Giving Rank 5-10 to Feature, %
Falling platelet count	201 (86.6)	6.5	6.1 (2.3)	24.6	61.6
Hyperferritinemia	194 (83.6)	7	6.5 (3.0)	39.2	53.9
Bone marrow hemophagocytosis	188 (81.0)	9	6.9 (3.6)	44.8	55.2
Increased liver enzymes	174 (75)	5	5.0 (2.4)	13	40.9
Falling leukocyte count	172 (74.1)	5	5.6 (2.5)	20.3	46
Persistent continuous fever ≥ 38°C	158 (68.1)	7	6.0 (3.4)	30.2	40.1
Falling erythrocyte sedimentation rate	142 (61.2)	6	5.5 (2.7)	15.9	38.8
Hypofibrinogenemia	142 (61.2)	5	5.4 (2.4)	12.9	36.6
Hypertriglyceridemia	135 (58.2)	5	5.1 (2.7)	16.8	31
Central nervous system dysfunction	104 (44.8)	5	5.0 (2.9)	11.6	23.7
Falling hemoglobin level	100 (43.1)	5	4.8 (2.3)	4.3	23.3
Prolongation of clothing times	81 (34.9)	4.5	4.5 (2.3)	4.7	17.2
Increased D-dimer	76 (32.8)	5	5 (2.6)	7.3	19.4
Hemorragic manifestations	72 (31.0)	5	5.3 (3.0)	10	17.7
Liver enlargement	71 (30.6)	4	4.8 (2.8)	7.3	14.2
Spleen enlargement	57 (24.6)	4	4.5 (2.8)	4.3	10.3
Increased lactic dehydrogenase	45 (19.4)	6	5.5 (2.6)	4.7	11.6
Increased soluble IL-2 receptor α	39 (16.8)	6	5.1 (3.1)	4.7	9.1
Increased soluble CD163	27 (11.6)	5	5.2 (3.0)	4.3	6
Lymphadenopathy	22 (9.5)	4	4.4 (2.9)	1.3	3.4
Decreased albumin	19 (8.2)	3	4.3 (2.9)	1.3	2.6
Hyponatremia	16 (6.9)	5	5 (3.2)	1.7	3.9
Arthritis improvement	14 (6.0)	2	3.1 (2.4)	0.9	0.9
Renal failure	13 (5.6)	2.5	3.6 (2.9)	0.9	1.7
Jaundice	9 (3.9)	5	5.9 (3.3)	1.7	2.2
Increased bilirubin	9 (3.9)	2	3.4 (2.0)	0	1.7
Respiratory failure	6 (2.6)	3	4.4 (3.0)	0.4	0.9
Cardiac failure	5 (2.2)	3	3.8 (2.6)	0	0.9

hypofibrinogenemia, and hypertriglyceridemia. These features consistently remained the 9 most frequently selected and most highly scored when respondents were stratified by continent. This makes it unlikely that differences of opinion between physicians from different countries will alter the validation process. The top 9 features identified in this phase of the project may be the best candidates to be part of the final set of diagnostic criteria for the syndrome.

Importantly, 7 of the 9 features rated as most important by respondents refer to laboratory abnormalities, whereas only 1 is a clinical manifestation. This is in keeping with the common view that early suspicion of MAS is most commonly raised by the detection of subtle laboratory changes, whereas clinical symptoms are often delayed[11]. Of the 8 criteria that are part of the preliminary guidelines for sJIA-associated MAS[11], only 5 (decreased platelet count, elevated liver enzymes, falling leukocyte count, hypofibrinogenemia, and evidence of macrophage hemophagocytosis in the bone marrow) entered the top 9 features, whereas all 3 clinical criteria (CNS dysfunction, hemorrhagic manifestations, and liver enlargement) did not. Considering the HLH diagnostic criteria[8], only 5 (fever, cytopenia, hypertriglyceridemia and/or hypofibrinogenemia, evidence of macrophage hemophagocytosis in the bone marrow, and hyperferritinemia) entered the top 9 features, whereas 3 [splenomegaly, low or absent natural killer cell activity, and increased soluble IL-2 receptor α (CD25)] did not. This observation suggests that both these guidelines may not be entirely adequate for the diagnosis of MAS complicating sJIA, particularly earlier in the course of the syndrome. Along these lines, late findings such as renal failure, respiratory failure, and cardiac failure received some of the lowest median rankings (Table 1).

Although, as stated above, pediatric rheumatologists from different continents revealed a fair agreement about the greater importance of the 9 top features, there were some differences in the frequency of feature selection. This suggests the existence of disparities in the awareness of the features of MAS or in the diagnostic approach to the syndrome, which highlights the utility of well established diagnostic guidelines.

As MAS is becoming better studied and defined, novel associations and tests are being used more readily to diagnose and monitor MAS. It has been recently suggested that soluble IL-2 receptor α (sCD25), reflective of T cell activation, and soluble CD163 (sCD163), related to activation of phagocytic macrophages/histiocytes, might be useful as diagnostic markers of MAS and helpful in monitoring dis-

Table 2. Comparison of percentage of respondents who selected each feature by continent.

Feature	Europe, N = 92	North America, N = 90	Other Continents, N = 50	p	Comparisons Significant on post-hoc Test*
Falling platelet count	81.5	92.2	86	0.1	
Hyperferritinemia	88	91.1	62	0.0002	EU vs OC
					NA vs OC
Increased liver enzymes	69.6	86.7	64	0.004	EU vs NA
					NA vs OC
Falling white blood cell count	70.7	82.2	66	0.07	
Bone marrow hemophagocytosis	79.3	81.1	84	0.8	
Persistent continuous fever ≥ 38° C	73.9	56.7	78	0.01	EU vs NA
					NA vs OC
Falling erythrocyte sedimentation rate	50	67.8	70	0.02	EU vs NA
Hypofibrinogenemia	63	64.4	52	0.3	
Hypertriglyceridemia	69.6	50	52	0.02	EU vs NA
Central nervous system dysfunction	53.3	32.2	52	0.009	EU vs NA
					NA vs OC
Falling hemoglobin level	34.8	47.8	50	0.1	
Prolongation of clotting times	20.7	44.4	44	0.001	EU vs NA
					EU vs OC
Increased D-dimer	18.5	48.9	30	0.0006	EU vs NA
Hemorrhagic manifestations	33.7	22.2	42	0.04	NA vs OC
Liver enlargement	41.3	15.6	38	0.0004	EU vs NA
					NA vs OC
Spleen enlargement	27.2	16.7	34	0.06	
Increased lactic dehydrogenase	26.1	17.8	10	0.06	
Increased soluble IL-2 receptor α	10.9	30	4	< 0.0001	EU vs NA
					NA vs OC
Increased soluble CD163	3.3	21.1	10	0.0008	EU vs NA
Generalized lymphadenopathy	14.1	3.3	12	0.03	EU vs NA
Decreased albumin	8.7	6.7	10	0.8	
Hyponatremia	15.2	2.2	0	< 0.0001	EU vs NA
					EU vs OC
Arthritis improvement	9.8	2.2	6	0.1	
Renal failure	4.3	5.6	8	0.7	
Increased bilirubin	4.3	2.2	6	0.5	
Jaundice	4.3	1.1	8	0.1	
Respiratory failure	3.3	2.2	2	0.9	
Cardiac failure	3.3	0	4	0.2	

* Pairs of comparisons that were statistically significant after Bonferroni correction for multiple comparisons. EU: Europe; NA: North America; OC: other continents.

ease activity and response to treatment[6,7]. These parameters may also help identify patients with sJIA with subclinical MAS[7]. However, more information is needed to ascertain whether their inclusion adds significantly to the use of the more traditional laboratory indicators of MAS. Notably, as these tests are often costly, they may not be available (or affordable) in many pediatric rheumatology centers, particularly in developing countries. In addition, if these ELISA tests for sCD25 and sCD163 are not ordered frequently in a particular hospital setting, they may not be run in a timely fashion to aid in early diagnosis of MAS.

We intentionally did not ask questionnaire respondents to indicate the threshold level for each laboratory test that they felt was optimal for early identification of MAS. This objective will be pursued in the subsequent phase of the project, which is under way to collect real data from patients with sJIA-associated MAS and patients with conditions that may be confused with MAS, including sJIA flare without MAS and febrile systemic infections. This process is also meant to enable a data-driven assessment of the relative sensitivity and specificity of clinical, laboratory, and histopathologic features in discriminating MAS from the conditions with which it may be confused. Notably, the data collection is structured in such a way that it may lead to understanding whether laboratory criteria for the syndrome are more worthy of being assessed in terms of absolute threshold values, or percentage change over the preceding days, or both. Ultimately, we hope to develop a (sJIA) disease-specific core set of criteria for diagnosis of MAS that is both highly sensitive and specific.

This study should be viewed in light of some potential limitations. The rate of response to our questionnaire survey

(45.9%) is in the low range of that obtained in similar initiatives performed previously in pediatric rheumatology, which varies from 49.8% to 80%[13,14,15,16,17,18,19,20]. However, previous surveys involved a much lower number of practitioners, up to 277. We mailed the survey to as many as 505 pediatric rheumatologists, who are currently part of the 3 largest international pediatric rheumatology research networks. Nevertheless, the relatively low response rate was expected, as MAS is a rare condition, likely to have been encountered or recognized only by physicians working in the largest tertiary care hospitals. However, since the number of respondents to our survey is the highest achieved so far in pediatric rheumatology, we feel that respondents were representative of pediatric rheumatologists internationally.

We identified the features of MAS that were felt to be the best potential diagnostic criteria for the syndrome in children with sJIA by a large sample of international pediatric rheumatologists. The diagnostic performance of these items will be scrutinized further in the next phase of the study, through analysis of real patient data.

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APPENDIX

List of study collaborators: MAS Study Group: Physician members who contributed in study planning and revised the format of the Delphi questionnaire: Edward M. Behrens (Philadelphia, USA), Susan Benseler (Toronto, Canada), Alexei A. Grom (Cincinnati, USA), Maria Martha Katsicas (Buenos Aires, Argentina), Bianca Lang (Halifax, Canada), Paivi Miettunen (Calgary, Canada), Seza Ozen (Ankara, Turkey), Athimalaipet Ramanan (Bristol, UK), Ricardo Russo (Buenos Aires, Argentina), Rayfel Schneider (Toronto, Canada), Gary Sterba (Caracas, Venezuela), and Carine Wouters (Leuven, Belgium).

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