FRI0541

HIGHLY ELEVATED FERRITIN LEVELS ARE ASSOCIATED WITH HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS/MACROPHAGE ACTIVATION SYNDROME – ARE WE MISSING TREATABLE DIAGNOSES? A RETROSPECTIVE SERVICE EVALUATION OF DIAGNOSIS IN PATIENTS WITH FERRITIN >10,000 MICROGRAM/L

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Background: Haemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS) is a hyperinflammatory syndrome potentially leading to critical illness. Early treatment reduces mortality but diagnosis requires a high index of suspicion. Highly elevated ferritin levels (HEF) >10,000 µg/L are highly specific for HLH/MAS [1] and should prompt consideration of hyperinflammation. Diagnostic guidelines for HLH, requiring the presence of ≥5/8 criteria [2], and classification criteria for MAS complicating systemic juvenile idiopathic arthritis (sJIA) have been published [3].

Objectives: To assess recognition of HLH/MAS in a paediatric population with HEF.

Methods: This retrospective study was conducted at 11 centres under local service evaluation permissions. Biochemistry databases identified patients ≤16 years with serum ferritin >10,000 µg/L during a 3-year period. Each case was assessed against the 2004 HLH criteria and, for patients with sJIA, the 2016 MAS criteria. Due to limited access to some of the laboratory tests, previously-published modified HLH criteria using a threshold of ≥4/5 (excluding tissue haemophagocytosis, decreased natural killer cell function, increased soluble interleukin-2 receptor) were also applied to all patients [4].

Results: 153 patients (55.6% male) were identified. Patient diagnoses included: infections (29.4%), rheumatological (17.0%) and malignancies (17.0%). A diagnosis of HLH/MAS was made by the treating clinical team in 39.9% and considered in a further 16.3%. Using all available data, 30/153 (19.6%) met ≥5/8 criteria and 93.3% of these patients were diagnosed with HLH/MAS by the treating team. 56 (36.6%) met ≥4/5 criteria and 33 (58.9%) of these were diagnosed with HLH/MAS by clinicians. HLH/MAS was not documented as being considered in the differential in 23.2%. Of 23 patients with sJIA, 82.6% met MAS classification criteria and 89.5% of these were diagnosed with MAS by the treating clinicians. Overall mortality was 32.7% (50/153) and was 27.9% (17/61) in patients diagnosed with HLH/MAS during their admission.

Conclusion: Although HEF is highly specific for HLH/MAS, the diagnosis was only made or considered in just over half of paediatric patients with this laboratory result. Increased awareness of this potentially-lethal condition is likely to lead to earlier treatment and reduced mortality.

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FRI0542

CLINICAL PRESENTATION, GENETIC ANALYSIS AND IFN-SCORE IN PATIENTS WITH UNDEFINED INTERFERONOPATHIES

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Background: In the last years, an expanding group of complex genetic disorders characterized by disturbance of the homeostatic control of IFN-mediated immune responses, have been identified, so called type I interferonopathies. An increased expression of type I IFN regulated genes, IFN signature (IS), is described in these conditions. IS represent a useful tool in clinical practice to classify patients with suspected interferonopathies.

Objectives: To evaluate the correlation between clinical presentation, genetic analysis and IFN-score in 10 patients with undefined interferonopathies

Methods: Patients with suspected interferonopathy based on the presence of typical clinical manifestations (neurological, muco-cutaneous symptoms), laboratory parameters (complement deficiency, low platelet count, presence of autoimmunity), instrumental abnormalities (cerebral calcification), were screened for the IFN-score. Defined IFN-mediated diseases were excluded. Patients presenting with a high IFN-score value (above a fixed cut-off of 10) underwent genetic screening by running a panel of 24 genes known to be involved in interferonopathies

Results: 10 patients with suspected interferonopathy followed in a single pediatric rheumatology center were included. 7/10 presented with recurrent episodes of fever (table). Patient 2, 3 and 7 displayed neurological manifestation, respectively epilepsy, epilepsy and mental retardation and progressive hemiplegia. To note epilepsy in patient 2 might be correlated to a bilateral intraventricular hemorrhage presented at birth. In two patients (1,4) gastrointestinal manifestation resembling inflammatory bowel diseases were described while patients 5,7 and 10 suffered from recurrent abdominal pain, diarrhea and patient 10 from hypertransaminasemia. Half of the patients complained arthromyalgia; arthritis developed in patient 2. Cutaneous involvement presented in 3 patients (1,3,6) respectively with a widespread panniculitis of trunk and limbs, aspecific vasculitis and Schonlein Henoch purpura. Other cutaneous manifestation were urticarial rash (pt 2) and an erythematous, desquamative confluent eczema (pt 4). Autoimmunity was confirmed in 2/10 patients. Two patients (4, 8) had an immunological defect with recurrent infections. The genetic analysis resulted negative in patients 1 and 7 and is still ongoing in patients 5, 6 and 8. Patients 2,3,4,9 and 10 carried one mutation in at least one IFN correlated gene not confirming the diagnosis. All patients presented an increased IS ranging from 14.2 to 172.5

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10
Systemic symptoms	Fever		Fever			Fever	Fever	Fever	Fever	Fever, haemophagocytic lymphohistiocytosis
CNS involvement		Epilepsy (bilateral asymmetric tonic clonus at birth)	Epilepsy, mental retardation					Hemiplegia		
Cerebral calcifications					/					
Gastrointestinal involvement	Erythema nodosum, specific IgE			Histological finding: mild RCU	Abdominal pain, diarrhea		Abdominal pain	/		Hypertransaminasemia
Skin/oculocutaneous involvement	Arthromyalgia, urticarial rash, pernio	Arthromyalgia, urticarial rash	Arthromyalgia, urticarial rash	Erythematous, desquamative confluent eczema	Arthromyalgia	erythema nodosum, Schonlein Henoch purpura in infancy	Arthromyalgia	/		
C3 (90-180 mg/dl)	144	127	81	113	53	137	96	203	97	83
C4 (10-40 mg/dl)	34	24	6	23	20	54	17	38	28	16
Immunodeficiency		ANA 1:2,560 Anti-dsDNA 1:640	ANA 1:10,240 Anti-dsDNA 1:1280	Immunodeficient ANA neg	Neg	/	Neg	Neg	Immunodeficient	/
WBC (mm ³)	5.2	4.4	9.8	3.9	4.6	8.1	6.4	4.4	3.5	1.7
Hb g/dl	10.4	12	12.9	10.2	13	11.1	14.1	12.1	16.5	9.7
PLT/mm ³	199	381	194	86	110	277	214	358	150	56
IFN signature	14.2	171.5	54.73	60.09	27.8	17.2	53.9	40.6	32.6	18.19
Genetic analysis	Neg	PSMBP1 p.Arg60Cys OTF1L1 p.Gln115His	CARD8 p.Leu309Phe	IFIH1 p.Arg374Gln	/	/	Neg	/	ACPS1 p.Arg309Tr	DNAH2 p.Ala45Gly

Conclusion: An elevated IFN-score represent a useful instrument in the clinical practice to classify patients with suspected interferonopathy. It may represent an important tool to select those patients to be genetically screened with a defined panel of interferonopathies correlated genes. In those patients in which the genetic analysis result negative, the presence