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A Systematic Review for the Management of the Genetically Defined Il-1-Mediated Autoinflammatory Diseases, Caps, Traps, Mkd and Dira

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present work aims to obtain clinical and analytical data that can guide us to an etiological diagnosis.

Objectives: To describe and identify the differences between HPS secondary to AID and HOD during their admission to a tertiary hospital between 2005 and 2019.

Methods: This is a retrospective observational study. We include patient meeting the diagnostic criteria for HLH proposed by Henter JI. (1), or who presented haemophagocytic cells (HC) in the bone marrow biopsy (BMB), or who had HPS in the hospital discharge report. Demographic, clinical, analytical, etiological, underlying disorders and prognosis variables were collected. Continuous variables are described with the mean or median according to the degree of normality. Kruskal Wallis, Fisher test and Mann-Whitney U test were used for the bivariate analysis, and also a multivariate logistic regression analysis was performed.

Results: We found 30 patients with secondary HPS, 22 of which corresponded to the AID [Systemic Lupus Erythematosus (n=5), Adult Still's Disease (n=3), Rheumatoid arthritis (n=1) and IgG4 Sclerosing Disease (n=1)] and HOD [Non-Hodgkin's Lymphoma (n=3), Myelodysplastic syndrome (n=3), Acute leukemia (n=3), Extranodal NK cell lymphoma (n=1), Multiple Myeloma (n=1) and probable lymphoproliferative process (n=1)]. The coincidence of an infectious disease with HPS was observed in 8 of the 22 cases [AID: 5 cases (2 *Cytomegalovirus*, 2 viral respiratory infections and 1 bacterial infection) and HOD: 3 cases (2 *Epstein Barr virus* and 1 bacterial infection)]. In two patients with HPS secondary to HOD (acute leukemia), allogeneic transplantation was associated as a possible trigger. In a patient with myelodysplastic syndrome, HPS was associated with the development of graft versus host disease. The age at diagnosis was lower in the AID [40 (26.5 - 56.3); p 0.001]. The HOD had more severe cytopenias [platelets 4500 (650 - 15,750; p 0.009), leukocytes 2050 (20 - 728; p 0.0001) and neutrophils 0 (0 - 280; p 0.002)]. Overall mortality (n=30 patients) was 43.3% (HOD: 66.7%; p 0.029) (table 1). In the final multivariate model according to AID and HOD, the following independent associations were observed: age (p 0.002), platelets (p 0.031), GOT (p 0.012), GPT (p 0.015), total proteins (p 0.007) and mortality (p 0.007).

Conclusion: The HOD presented higher mortality and severe cytopenias. The AID presented a higher elevation of transaminases and better prognosis.

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[1] Henter JI, et al. HLH-2004: Diagnostic and therapeutic guidelines for HLH. Pediatr Blood Cancer. 2007;48:124.

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FRI0482

A SYSTEMATIC REVIEW FOR THE MANAGEMENT OF THE GENETICALLY DEFINED IL-1-MEDIATED AUTOINFLAMMATORY DISEASES, CAPS, TRAPS, MKD AND DIRA

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Background: Ultra-rare genetically defined IL-1 mediated autoinflammatory diseases (AIDs) include mevalonate kinase deficiency (MKD), tumor necrosis factor receptor associated periodic syndrome (TRAPS), cryopyrinopathies (CAPS) and deficiency of the IL-1 receptor antagonist (DIRA). These disorders start perinatally, the clinical disease manifestations include systemic inflammation; and late diagnosis and inappropriate treatment cause irreversible organ damage. The varying skills of treating rheumatologists and paediatricians illustrate the need for management guidance, however criteria for validated methodology is geared towards common diseases with more heterogeneous pathogenesis.

Objectives: The focus of this systematic review includes the evaluation of the existing literature and the evaluation of existing EULAR methodology for use in the ultra-rare diseases with defined pathomechanisms, CAPS, TRAPS, MKD and DIRA

Methods: EULAR standardized operating procedures were followed during the review, including a meeting of experts to discuss key words, inclusion/exclusion criteria and PICO questions. Three fellows established the protocol of the review under the supervision of the EULAR methodologist and PubMed, Embase, and Cochrane databases were searched up to September 30, 2019.

Results: We found 1582 articles for CAPS, 1109 articles for TRAPS,1741 articles for MKD and 557 articles for DIRA. Duplications, animal models and basic science studies, conference papers, systematic reviews/meta-analysis and articles not in English language is excluded. If we excluded case reports (n<4), then 72 articles for CAPS, 40 articles for TRAPS,44 articles for MKD and 1 article for DIRA should be included for full text evaluation and data extraction (Figure 1). However among the case reports, patients excluded achieved complete remission, assessed by clinical criteria and biomarkers. Of the studies included only few randomized studies for CAPS, TRAPS, MKD, and DIRA and would achieve higher level of evidence (Figure 1).

Conclusion: CAPS, TRAPS, MKD and DIRA are monogenic diseases with defined pathways and outcomes that include inflammatory remission based on clinical and biomarker data. Current methodological evaluations for genetically complex diseases undervalue the published evidence in case reports that report on remission and IL-1 biomarkers. We suggest that case studies that include hard outcomes including **inflammatory remission, and open label withdrawal studies that are both backed by biomarkers could be allowed to be included and be considered for a stronger evidence level.**

Table 1. Characteristics and comparative analysis of HPS secondary to AID and HOD

	Total		AID		HOD		
n	30		10		12		*p<0,05
Age (*x* ± s)	55,5	±18,3	40	26,5-56,3	68	57,5-73,8	0,001
Gender, male	14	46,7%	3	30%	9	75%	0,084
Spenomegaly	16	53,3%	5	50%	8	66,7%	0,666
Hepatomegaly	10	33,3%	4	40%	4	33,3%	1,000
Hb (g/dL)	7,1	6,4-7,9	7,2	6,6-8,4	6,5	5,9-7,3	0,05
Pt (x10^9/L)	13 500	5 000-52 500	31 650	11 000-100 250	4 500	650-15 750	0,004
Leu (x10^9/L)	1 250	238-3 153	1 985	1 350-3 382	185	20 – 728	0,000
Neu (x10^9/L)	615	0-1 550	948	633-1 808	0	0-280	0,001
Fb (mg/dL) (n=24)	171	111-358	212	90-450	167	114-354	1,00
Fer (ng/mL) (n=28)	15 330	5 434-38 284	14 263	4 254-14 263	16 796	8 287 - 56 969	0,314
Tg (mmol/L)	341	226-438	411,5	234-572	321	233,8-403,8	0,314
GOT (U/L)	139	78-406	457	289-1 140	106	71-193	0,003
GPT (U/L)	162	46-388	432	174-599	109	54-263	0,017
T.P. (n=29)	4,8	±,1,04	5,0	4,5-5,8	4,3	3,9-4,5	0,003
Hospital stay	35,5	20,0-60,8	30,5	9,5-53,3	61,5	29,3-93,3	0,036
Hospital stay pre-dx	16,5	8,5-29,8	10	5,0-16,5	26	10-39	0,038
Mortality	13	43,3%	1	10%	8	66,7%	0,011

Hb: hemoglobin, Pt: platelets, Leu; leukocytes, Neu, neutrophils, Fb: fibrinogen, Fer: ferritin, Tg: triglycerides, GOT: aspartate aminotransferase, GPT: alanine aminotransferase, T.P.: total proteins, pre-dx: prior to the diagnosis of HPS according to BMO. *Analysis between AID and HOD.

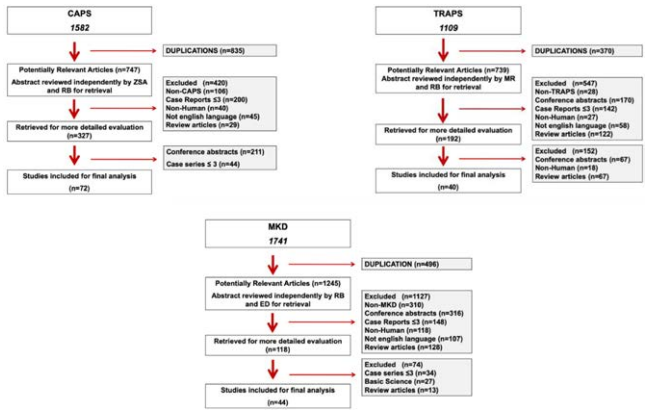

Figure 1. Flow-charts of systematic review for CAPS, TRAPS and MKD.

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FRI0483 SUBCLINICAL INFLAMMATION AND RELATED PARAMETERS IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

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Background: Familial Mediterranean Fever (FMF), which is more common in groups in the Mediterranean basin, is a monogenic autoinflammatory disease characterized by recurrent attacks of febrile peritonitis, pleuritis and arthritis.

Objectives: In this study, we aimed to investigate the clinical, demographic and genotypic features that may be associated with subclinical inflammation in FMF and to determine the related parameters with subclinical inflammation.

Methods: FMF patients according to the Tel-Hashomer criteria were included into the study. The demographic characteristics of the patients, duration of the disease, concomitant diseases, MEFV genotype mutation, colchicine use and resistance were collected. Acute-phase reactants such as white blood cell count, erythrocyte sedimentation rate, and C-reactive protein levels during the attacks and attack-free periods were noted. Subclinical inflammation was defined as the continuation of the acute phase response (CRP) between episodes. We divided study population into two groups as; patients with or without subclinical inflammation (Group 1 and Group 2, respectively) and these group were compared with the parameters described above. Patients with infectious disease (viral or bacterial) in the past two months were excluded from the study

Results: Eigthy patients (72.5% female) with mean age 37.1 SD 11.2 years were recruited into the study. Twenty-three (28.7%) patients were determined with subclinical inflammation. Group 1 had significantly higher rate of concomitant rheumatic disease(i.e spondyloarthropathy), erythrocyte sedimentation rate and MEFV homozygous mutation compared with Group 2 ($p<0.05$, for each). Disease duration, months PRASS score, FMF quality of life, age at onset of symptoms, family history of FMF, response to colchicine, attack time, attack in the last 6, delay in diagnosis parameters were not significantly different between groups ($p> 0.05$).

Conclusion: FMF patients whose elevated erythrocyte sedimentation rate and MEFV homozygous mutation should be closely monitored for subclinical inflammation even during attack-free periods. Concomitant disease should be detected in FMF patients with subclinical inflammation.

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Table 1: Demographic and clinical features of the patients with familial Mediterranean fever

	Without Subclinical inflamation n= (57)	With Subclinical inflamation n= (23)	P value
Age (years; mean SD)	37,78 SD 13,22	36,82 SD 10,49	0.987
Female, gender, n (%)	45(%78)	13(%56)	0.055
Disease duration (month; mean SD)	255,3 SD 195,1	180,2 SD 121,1	0.191
PRASS score (mean SD)	6,08 SD 2,15	5,36 SD 1,59	0.147
BMI, kg/m^2	26,12 SD 4,8	32,13 SD 28,48	0.629
Current smoking status (%)	17(%29)	3(%13)	0.067
Age at onset of symptoms (month; mean SD)	15,69 SD 9,41	17,28 SD 10,34	0.54
Family history of FMF(%)	37(%64)	18(%78)	0.295
Response to colchicine(%)	6(%10)	4(%17)	0.462
Attack time (day; mean SD)	1,9 SD 1,1	2,26 SD 1,4	0,523
Attack in the last 6 months (mean SD)	2,79 SD 3,1	4,56 SD 5,5	0,184
FMF quality of life (mean SD)	31,5 SD 13,6	25.7 SD 16,4	0,130
Delay in diagnosis(month; mean SD)	12,29 SD 10,9	14,3 SD 14,9	0,840

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FRI0484 SAFETY PROFILE, CLINICAL AND RADIOLOGICAL EFFICACY OF ANAKINRA, TARGETED AND COMBINED TREATMENT IN ERDHEIM-CHESTER DISEASE

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Background: Erdheim-Chester disease (ECD) is a rare non-Langerhans histiocytosis. Combined treatment with anakinra (ANK) and targeted MAPK-inhibiting therapies (vemurafenib – VMF - or cobimetinib - CBM) has been recently used to treat severe cases of ECD.

Objectives: To evaluate the safety and the clinical and radiological efficacy of ANK, targeted and combined treatments in ECD patients in a real-world setting.

Table 1. Disease characteristics and therapy-related adverse reactions of Erdheim-Chester patients treated with vemurafenib, cobimetinib and/or anakinra.

	Vemurafenib (n=19)	Cobimetinib (n=10)	Anakinra (n=12)
Clinical Manifestations			
Cardiovascular	79%	70%	75%
Retroperitoneal	84%	60%	42%
Pleuropulmonary	63%	80%	42%
Neurological and/or orbital	90%	90%	92%
Adverse reactions	74%	60%	25%
Renal	26%	10%	0%
Cutaneous	26%	30%	17%
Systemic Inflammation	11%	10%	0%
Cardiovascular	11%	10%	0%
Gastrointestinal	0%	30%	0%
Haematological	0%	10%	0%
Herpes Zoster	0%	0%	8%