Objectives: Our study aimed to compare the accuracy of serum biomarkers for the diagnosis of MAS complicating s-JIA and to investigate the clinical significance of serum neopterin levels as an indicator of disease activity and diagnosis of MAS complicating s-JIA.

Methods: Serum cytokine levels (neopterin, IL-18, and CXCL9 and soluble tumor necrosis factor receptor type I (sTNFR-I) and II were determined by enzyme-linked immunosorbent assay in 78 patients with s-JIA, including 21 with MAS. The accuracy of these levels for the diagnosis of MAS were compared. Next, serum neopterin levels, in total 125 patients with s-JIA, including 30 with MAS, 15 with Epstein-Barr virus-induced hemophagocytic lymphohistiocytosis (EBV-HLH), and 15 with Kawasaki disease (KD), as well as 28 healthy controls (HCs) were analysed. Results were compared with the clinical features of MAS.

Results: Receiver operating characteristic curve analysis revealed area under the curve values and cut off values of neopterin, IL-18, CXCL9, sTNFR-II/I ratio and ferritin were 0.9465/19.5nmol/l, 0.8895/69250ng/ml, 0.9333/3130pg/ml, 0.9395/3.796 and 0.8671/2560ng/ml, respectively. Serum neopterin levels were significantly elevated in patients with MAS and EBV-HLH compared with those in patients with acute-phase s-JIA and KD. Serum neopterin levels profoundly and rapidly increased as MAS developed and correlated positively with disease activity.

Conclusion: Serum neopterin levels may be used as a promising indicator of disease activity in s-JIA and MAS and for evaluating it. It may also be a useful marker to diagnose the transition to MAS from active-phase s-JIA.

REFERENCES:

- [1] Huber C, et al. J Exp Med 1984;160:310-6.
- [2] Bracaglia C, et al. Ann Rheum Dis 2017;76:166-72.
- [3] Shimizu M, et al. Clin Exp Immunol 2018;191:349-355.

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FRI0536

FAMILIAL MEDITERRANEAN FEVER (FMF): A SINGLE CENTER EXPERIENCE FROM TURKEY

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Background: Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease mainly affecting ethnic groups living at Mediterranean region. Since the discovery of the *Mediterranean Fever (MEFV)* gene, molecular genetic testing has been used as a diagnostic adjunct especially in atypical cases (1, 2). Although substantial progress had been achieved about the etiopathogenetic mechanisms of FMF during the past 20 years, the diagnosis is still based on clinical criteria.

Objectives: To define the demographic, clinical and laboratory characteristics of children with FMF and then to compare the identification capacity of 3 validated FMF diagnostic criteria (Tel-Hashomer, Livneh and Pediatric) at our cohort (3-5).

Methods: The medical records of 1685 children diagnosed and followed up as FMF were reviewed retrospectively. All patients were evaluated for three diagnostic criteria.

Results: A total of 1685 children (839 girls, 846 boys) were involved to the study. Family history of FMF was positive in 46.1%. The mean $\pm$ standard deviation of current age, age at symptom onset, age at diagnosis were 13 $\pm$ 5.4, 5.4 $\pm$ 4.05, 7.9 $\pm$ 4.1 years, respectively. Median (min-max) follow-up period was 3 (0.5-18) years. Among 1685 patients, 82.8% had fever, 78.2% had abdominal pain, 36.1% had arthritis, 22.6% had chest pain and 16.6% had erysipelas-like erythema. Three patients had biopsy proven amyloidosis. Concomitant disease was present in 140 (8.3%) patients. Most of them (40.7%) were diagnosed with juvenile idiopathic arthritis and FMF. Henoch-Schönlein vasculitis was observed in 35 (2.5%) patients. Median (min-max) PRAS score was 7 (3-13). Forty-four patients (2.6%) were unresponsive to adequate doses of colchicine. Among them, 16 (36.4%) were treated with anakinra and 28 (63.6%) received canakinumab. Children homozygous for M694V were found to have more severe course of disease and higher PRAS scores ($p < 0.001$). Furthermore, 34 (77.3%) of colchicine resistant patients carried at least one M694V variant. When we applied the diagnostic criteria to our cohort, 99.5% met the Livneh criteria, 91.6% fulfilled the pediatric criteria and 82.9% satisfied the Tel-Hashomer criteria.

Conclusion: This is the largest pediatric cohort studied and presented since now. We believe that the large number of our cohort is convincing at the point of discussing phenotype-genotype relations. We confirmed

that carrying M694V mutation is associated with increased disease severity. On the other hand, we compared two adult and one pediatric validated diagnostic criteria at a largest group of children with FMF.

REFERENCES:

- [1] Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. The International FMF Consortium (1997). Cell 90:797-807
- [2] A candidate gene for familial Mediterranean fever (1997). Nat Genet 17:25-31.
- [3] Sohar E, Gafni J, Pras M, Heller H (1967) Familial Mediterranean fever. A survey of 470 cases and review of the literature. The American journal of medicine 43:227-253
- [4] Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, Migdal A, Padeh S, Pras M (1997) Criteria for the diagnosis of familial Mediterranean fever. Arthritis and rheumatism 40:1879-1885.
- [5] Yalcinkaya F, Ozen S, Ozcakar ZB, Aktay N, Cakar N, Duzova A, Kasapcopur O, Elhan AH, Doganay B, Ekim M, Kara N, Uncu N, Bakkaloglu A (2009) A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. Rheumatology (Oxford, England) 48:395-398.

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FRI0537

LONG-TERM OUTCOMES AND TREATMENT EFFICACY IN PATIENTS WITH TNF RECEPTOR-ASSOCIATED AUTOINFLAMMATORY SYNDROME (TRAPS): A SERIES OF 290 CASES FROM THE EUROFEVER/EUROTRAPS INTERNATIONAL REGISTRY

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Background: Tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is one of the best known monogenic auto-inflammatory disorder resulting from an autosomal dominant variation in the TNF super family receptor 1A (*TNFRSF1A*) gene.

Objectives: To define best treatment approach in patients with TRAPS and effect on long-term outcomes.

Methods: We reviewed all data on patients with *TNFRSF1A* variants enrolled in the Eurofever/EUROTRAPS international registry.

Results: Data on 290 patients were available. Patients with R92Q, P46L or intronic variants (49%) displayed milder disease than 147 patients with mutations affecting other coding regions, with less frequent abdominal pain and skin rashes ($P < 0.01$), higher efficacy rate of colchicine as maintenance treatment, and none developed AA amyloidosis. Almost 90% of patients with exon mutations required maintenance therapy. Anti-interleukin (IL) 1 β drugs were the most frequently used (47 patients), with the highest efficacy rate ($>90\%$ complete response), while Etanercept was less effectively used and discontinued in 72% of patients. No patients on anti-IL1 β treatment developed amyloidosis and 10 patients with amyloidosis have been successfully treated with anti IL-1 agents with preservation of native renal function in 7 and excellent long-term transplant function in 2. Nine women had a history of failure to conceive and seven had successful pregnancies without fertility treatment following complete disease control with anti-IL1 β drugs. Long term safety profiles for anti IL-1 agents were excellent even in the presence of comorbidity.

Conclusion: Anti-IL1 β drugs are the best maintenance treatment in TRAPS with potential to reverse the most serious disease complications of AA amyloidosis and infertility. The diagnosis of TRAPS should be considered very carefully in patients carrying R92Q, P46L or intronic *TNFRSF1A* variants.

REFERENCES:

- [1] Lachmann HJ, Papa R, Gerhold K, Obici L, Toutou I, Cantarini L, et al. The phenotype of TNF receptor-associated autoinflammatory syndrome (TRAPS) at presentation: a series of 158 cases from the Eurofever/EUROTRAPS international registry. Annals of the rheumatic diseases. 2014;73(12):2160-7.
- [2] Papa R, Doglio M, Lachmann HJ, Ozen S, Frenkel J, Simon A, et al. A web-based collection of genotype-phenotype associations in hereditary

recurrent fevers from the Eurofever registry. Orphanet Journal of Rare Diseases. 2017;12(1):16.

- [3] Papa R, Lachmann HJ. Secondary, AA, Amyloidosis. Rheum Dis Clin North Am. 2018;44(4):585–603.

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FRI0538

MAY SOME OF THE MEFV GENE VARIANTS CAUSE PFAPA SYNDROME LIKE SYMPTOMS?

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Background: PFAPA syndrome is characterized by periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis. As diagnosis usually depends on clinical diagnostic criteria, sometimes it can be difficult to distinguish this clinical entity from the other periodic fever syndromes, especially in regions endemic for FMF.

Objectives: The objective of the study is to evaluate the PFAPA patients' MEFV gene variation frequencies (if it was performed) and relations between detected variants and clinical manifestations in pediatric PFAPA patients.

Methods: Nine hundred and thirty-seven patients that were recorded to our database as PFAPA syndrome were evaluated. Patients were reached by phone and asked about characteristics of their fever episodes, presence of acute phase reactant elevation, pharyngitis, aphthous stomatitis/cryptic tonsillitis, cervical lymphadenopathy, arthralgia, arthritis, abdominal pain, headache, nausea or vomiting, chest pain, diarrhea, skin changes, myalgia and conjunctivitis in the course of fever attack, if they had tonsillectomy, if they were attack-free after tonsillectomy and if they had clinical response to steroid or colchicine.

Results: There were 937 PFAPA patients in our database. MEFV gene analysis was performed in 407 (%43) of PFAPA patients and 305 of them had at least one mutation. Most common MEFV mutations of patients were: R202Q heterozygotes (25,9%), M694V heterozygotes (24,2%), E148Q heterozygotes (13,4%), P369S heterozygotes (9,8%) and V726A heterozygotes (8,6%), respectively.%45.8 of detected mutations were located in exon 2,%40,3 of them were located in exon 10 and% 13,9 of them were located in exon 3 of the MEFV gene. Patients were divided into five groups according to their mutations' localization and groups were compared according to clinical features. There were significant differences between groups according to presence of pharyngitis, arthralgia, abdominal pain, myalgia and tonsillectomy history (Table 1).

Table 1. Comparison of patients according to their mutations' location and clinical features.

		Exon 2	Exon 3	Exon 10	No Mutation	MEFV study not performed	p
Pharyngitis	Yes	21	9(40,9)	45	28 (87,5)	168(87,5)	<0,05
	No	(87,5)	13 (59,1)	(80,4)	4(12,5)	24(12,5)	
Aphthous stomatitis/Cryptic tonsillitis	Yes	15	8(36,4)	21	17 (53,1)	102(53,1)	0,11
	No	(62,5)	14 (63,6)	(37,5)	15(46,9)	90(46,9)	
Cervical lymphadenopathy	Yes	10	8(36,4)	21	14(56,3)	77(40,1)	0,97
	No	(41,7)	14 (63,6)	(37,5)	18(43,7)	115(59,9)	
Arthralgia	Yes	5(20,8)	11(50)	22	19(59,4)	66(34,5)	0,02
	No	19 (79,2)	11(50)	(39,3)	13(40,6)	126(65,5)	
Abdominal Pain	Yes	17	12	27	16(50)	56(70,8)	<0,05
	No	(70,8)	(54,5)	(48,2)	16(50)	136(29,2)	
Myalgia	Yes	0(0)	8(36,4)	9(16,1)	7(21,9)	24(12,5)	0,006
	No	24(100)	14 (63,6)	47 (83,9)	25(78,1)	168(87,5)	
Tonsillectomy	Yes	14	5(22,7)	21	20(62,5)	109(57,1)	0,005
	No	(58,3)	17 (77,3)	(38,9)	12(37,5)	82(42,9)	

Conclusion: In this study, we reported increased frequency of MEFV mutations in a large PFAPA patients cohort. Frequency differences of clinical features between groups suggest that some of the MEFV gene mutations may modify phenotype of PFAPA syndrome. Furthermore, underlying MEFV gene mutations possibly lead to PFAPA like clinical presentation in FMF patients. Another remarkable finding of this study is the relatively high P369S mutation rates in patients with PFAPA syndrome.

REFERENCES:

- [1] Pehlivan E, Adrovic A, Sahin S, et al. (2018). PFAPA Syndrome in a Population with Endemic Familial Mediterranean Fever. The Journal of pediatrics, 192, 253-255.
- [2] Yamagami K, Nakamura T, Nakamura R, et al. (2017). Familial Mediterranean fever with P369S/R408Q exon3 variant in pyrin presenting as symptoms of PFAPA. Modern rheumatology, 27(2), 356-359.

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FRI0539

WNT6 MUTATION CAUSES AN EARLY ONSET GRANULOMATOUS INTESTINAL DISEASE WITH RECURRENT HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

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Background: Use of NGS in patients with unclassifiable disease lies a possible approach to the identification of novel disease causing genes.

Objectives: We report a patient with an early onset inflammatory bowel disease with granulomatous lesions and recurrent HLH episodes carrying a missense mutation in the WNT6 gene.

Methods: A trio based Whole Exome Sequencing (WES) approach was used. Cytokine levels were measured by multiplex assay and by specific ELISAs.

Results: Ten years old Caucasian boy affected by early onset pan-colitis from 9 months of age. Since the disease onset the patient is on glucocorticoid treatment with amino acid enteral nutrition and oligo antigenic diet. Because of recurrent disease relapses at any attempt of glucocorticoid withdrawal, azathioprine and cyclosporine treatments were also added. At 2 years of age he received total colectomy with ileostomy.