

Attacks of TNF-receptor associated periodic syndrome are associated with higher inflammatory markers than familial Mediterranean fever

Sirs,

TNF receptor-associated periodic syndrome (TRAPS) and familial Mediterranean fever (FMF) are two monogenic auto-inflammatory diseases presenting with recurrent febrile episodes characterised by serositis, skin eruptions, arthralgia, and/or myalgia (1, 2). Despite their similarity in presenting signs and symptoms, they have some distinctive clinical characteristics. While TRAPS has no ethnic predilection and presents with attacks generally lasting over one week (1), FMF almost exclusively affects individuals of Mediterranean origin with attacks generally resolving within 72 hours (2). Furthermore, in our experience, TRAPS patients display marked leukocytosis with a left shift and a significant elevation in inflammatory markers during attacks, while this is more variable in FMF patients. To verify this clinical impression, we compared values of serum leukocytes, neutrophils, and C-reactive protein (CRP) during attacks between TRAPS and FMF patients.

We retrospectively screened for eligibility adult patients with TRAPS and FMF from the database of the French Reference Center for Auto-inflammatory diseases and AA Amyloidosis (CEREMAIA). For inclusion, clinical diagnosis of TRAPS had to be supported by the presence of a class 4 or 5 pathogenic variant in the *TNFRSF1A* gene; clinical diagnosis of FMF was based on the Livneh criteria (2) and supported by homozygosity or compound heterozygosity for class 4 or 5 pathogenic variants in the *MEFV* gene. Patients were excluded if they presented the following conditions: active comorbid inflammatory disease, infection, or neoplasia, haematologic disease, advanced cirrhosis, splenectomy, or pregnancy. Medical charts were reviewed for the highest values of serum leukocytes, neutrophils, and CRP measured during an auto-inflammatory attack, as well as for the presence of confounding factors (corticosteroid use, smoking status, and body mass index (BMI)). Unadjusted comparisons were performed with Student's t-test for quantitative variables and Fisher's exact test for binary variables. Comparison of leukocytes, neutrophils, and CRP was then adjusted for confounding factors using linear regression. Candidate cut-off values for leukocytes, neutrophils, and CRP above which a diag-

Table I. Patients' features.

	FMF (n=50)		TRAPS (n=23)		Unadjusted p-value	Adjusted p-value*
	Available data	Mean (SD) or number (percentage)	Available data	Mean (SD) or number (percentage)		
Age, years	50	36.8 (9.6)	23	41.9 (17.4)	0.11	-
Female	50	25 (50%)	23	14 (61%)	0.27	-
BMI, kg/m ²	50	23.6 (3.9)	17	25.7 (4.6)	0.07	-
Smoking	34	10 (29%)	8	0 (0%)	0.09	-
Corticosteroid use	50	0 (0%)	16	4 (25%)	0.002	-
Leukocytes, G/L	49	10.5 (3.9)	21	19.6 (10.5)	<0.001	<0.001
Neutrophils, G/L	45	7.7 (3.8)	17	14.3 (5.0)	<0.001	<0.001
CRP, mg/L	49	125 (67)	22	186 (93)	0.02	0.001

FMF: familial Mediterranean fever; TRAPS: TNF-receptor associated periodic syndrome; SD: standard deviation; BMI: body mass index; CRP: C-reactive protein.

*adjusted for BMI and corticosteroid use.

nosis of TRAPS was more probable than FMF were calculated using a ROC curve analysis for a positive likelihood ratio >5. A total of 23 TRAPS and 50 FMF patients were included (Table I). All TRAPS patients presented with leukocytosis (leukocytes >10 G/L) and 94% with a left shift (neutrophils >7 G/L). Differences in leukocytes, neutrophils, and CRP values remained significant between TRAPS and FMF patients after adjusting for corticosteroid use and BMI. Adjustment for smoking status could not be performed due to missing data. Areas under the ROC curves for the differential diagnosis between FMF and TRAPS were 0.88 [95% confidence interval (CI): 0.80, 0.96] for leukocytes, 0.68 [95% CI: 0.55, 0.82] for neutrophils, and 0.87 [95% CI: 0.78, 0.96] for CRP. Leukocytes $\geq 18 \times 10^9/L$, neutrophils $\geq 14 \times 10^9/L$, and CRP ≥ 250 mg/L strongly favoured a diagnosis of TRAPS over FMF (Supplementary Fig. S1), with positive likelihood ratios of 11.7 [95% CI: 2.8, 48.7], 6.0 [95% CI: 2.1, 16.8], and 6.7 [95% CI: 1.5, 30.5], respectively.

In clinical practice, when a patient presents with recurrent episodes of fever and abdominal pain or myalgia lasting more than 3 days, the distinction between TRAPS and FMF can be difficult, resulting in inappropriate genetic testing, diagnostic delay, and suboptimal treatment. Our data show that serum leukocytes, neutrophils, and CRP values measured during an inflammatory attack are higher in TRAPS than in FMF. These findings should be confirmed in future studies that specifically include patients with a problematic clinical phenotype, such as those with intermediate length of attacks (between 3 and 7 days). TRAPS attacks appear to be associated with higher serum leukocyte, neutrophil, and CRP values than FMF, however, the diagnosis should be based solely on genetic analysis.

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References

- LACHMANN HJ, PAPA R, GERHOLD K *et al.*: The phenotype of TNF receptor-associated auto-inflammatory syndrome (TRAPS) at presentation: a series of 158 cases from the Eurofever/EURO-TRAPS international registry. *Ann Rheum Dis* 2013; 73: 2160-7.
- LIVNEH A, LANGEVITZ P, ZEMER D *et al.*: Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997; 40: 1879-85.