Circulating intercellular adhesion molecule 1 (sICAM-1) in tumour necrosis factor receptor-associated periodic syndrome (TRAPS)

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Tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is an autosomal dominant autoinflammatory disease caused by mutations in the *TNFRSF1A* gene, encoding for the receptor of TNF-α. It is clinically characterised by recurrent fever episodes typically lasting more than 1 week combined with inflammatory manifestations involving several organs and tissues (1). The disease can be caused by high-penetrance mutations leading to more severe disease manifestations, and low-penetrance variants generally contributing to the development of a milder phenotype (2). Among disease manifestations, an increased cardiovascular risk has been suggested for TRAPS (3): a large European study involving 95 subjects with premature myocardial infarction (MI) and a first grade family history for MI suggested that the presence of the low-penetrance R92Q mutation on the *TNFRSF1A* gene was positively associated with the presence of atherosclerotic carotid plaques and an increased carotid intima-media thickness, possibly predisposing to atherosclerosis and coronary artery complications (4). In addition, Stojanov *et al*. described two patients with a *TNFRSF1A* mutation on the cleavage site of the receptor developing a MI and an arterial thrombosis, respectively (5). Accordingly, in TRAPS patients the development of endothelial dysfunction and atherosclerosis could be related to an impaired bradykinin- and acetylcholine-induced vasodilatation induced by TNF-α and potentiated by a prolonged inflammatory state (6).

In support of these data, we have found serum intercellular adhesion molecule 1 (sICAM-1) significantly higher in 39 serum samples obtained from 27 TRAPS patients compared to 33 age- and sex-matched healthy controls (HC) (p=0.0017). When patients were distinguished according to their mutations, we found that sICAM was significantly higher in both samples from patients carrying high penetrance mutations (C114W: 1/39; C125R: 2/39; C43R: 4/39; C43Y: 2/39; C52Y: 4/39; C55Y: 1/39; delta103-104del: 2/39; L167-G175del: 1/39; S59N: 1/39; S59P: 3/39; T50M: 8/39) (p=0.0067) and low-penetrance variants (R92Q: 5/39; R104Q: 1/39; D12E: 2/39; V95M: 2/39) (p=0.0146). Conversely, no differences were found between patients carrying high-penetrance and low-penetrance mutations (p=0.21).

Moreover, sICAM was significantly higher in TRAPS patients than HC disregarding disease duration (p=0.0081) and the occurrence of systemic amyloidosis (p=0.0036). Conversely, patients with increased serum amyloid A (SAA) and C-reactive protein (CRP) showed significantly higher sICAM concentrations than HC (p=0.0066 and p=0.0092, respectively), but this was not the case for patients with negative SAA and CRP (p= 0.06 and p=0.12, respectively). Interestingly, when patients were subdivided into males and females we noted that sICAM was significantly higher in male TRAPS patients than male HC (p=0.0108), but no significant differences were found between female TRAPS patients and female HC (p=0.1269). Nevertheless, no differences were identified in sICAM-1 levels between male and female patients (p=0.26). These findings are graphically showed in Figure 1.

No statistical differences were found between patients administered with biologic agents (TNF-α or interleukin-1 inhibitors) and patients nor already under therapy (p=0.25). Similarly, as already reported for sICAM-1 (6), no differences were identified in relation to body mass index (p=0.72). Table I describes demographic and clinical data of patients enrolled.

According to previously reported data, soluble form of sICAM-1 is increased in the serum of patients at high risk for cardiovascular diseases (6, 7). In this regard, our findings support the hypothesis of an increased propensity for atherosclerotic-related complications in patients with TRAPS. Moreover, since high CRP and SAA levels constitute cardiovascular risk factors (8, 9), the significant increase of sICAM only in patients with raised values of these inflammatory markers may further suggest an increased cardiovascular risk in TRAPS.

Furthermore, although the number of samples from untreated patients was small compared to those treated (8 *versus* 31, respectively), there was no statistical difference between treated and untreated patients, thus indicating that treatment does not affect sICAM-1 levels. Overall, these results seem to suggest an increased cardiovascular risk in TRAPS patients also when disease activity is under control. Another interesting finding is related to the lack of differences in sICAM-1 levels between patients with high- and low-penetrance mutations, which supports cardiovascular risk is not related to disease activity in TRAPS.

Although a relatively high concentrations is found in different inflammatory diseases (7), the role of sICAM-1 in the inflammation is currently poorly understood. It appears transcriptionally up-regulated in response to interleukin-1, which has a pivotal role in TRAPS (10). However, in this study 29 out of 39 samples were collected during interleukin-1 inhibition without affecting sICAM levels. Consequently, further studies are warranted to clarify the relevance of this soluble protein in the regulation of the inflammatory response; the possible long-term consequences hidden behind the increase of this marker of cardiovascular risk; why sICAM-1 remains increased disregarding clinical disease activity and treatment in TRAPS patients; and whether biologic agents work downstream of sICAM-1 counteracting it's *in vivo* function.

Table I. Summary of demographic and clinical data of TRAPS patients enrolled. Data are expressed as mean ± standard deviation (SD).

	HC	TRAPS	LP-TRAPS	HP-TRAPS
Age (yers)	42,21 ± 13,17	43,74 ± 12,77	47,43 ± 7,35	42,45 ± 14,12
Gender (F/M)	14/19	10/17	3/4	7/13
Disease onset (years)	-	20,63 ± 19,10	43,29 ± 9,924	12,7 ± 14,34
Duration of disease (years)	-	22,74 ± 18,54	4,14 ± 5,187	29,25 ± 16,92
Number of attacks per year	-	5,63 ± 4,78	2,86 ± 4,606	6,6 ± 4,26
Attacks duration (days)	-	9,74 ± 6,86	10,57 ± 9,882	9,45 ± 5,39
Serum amyloid-A levels (mg/L)	-	187,74 ± 483,77	78,73 ± 78,91	224,07 ± 556,1
CRP (mg/dl)	-	2,15 ± 3,29	2,26 ± 3,81	2,12 ± 3,26
Amyloidosis (present/absent)	-	5/27	0/7	5/15
BMI kg/m^2	-	24,05 ± 3,59	24,13 ± 2,71	24,02 ± 3,91
Patients on biologic treatment	-	20/27	4/7	16/20

BMI: body mass index; CRP: C-reactive protein; F: female; HC: healthy controls; HP: high-penetrance; LP: low-penetrance; M: male; TNF: tumour necrosis factor.

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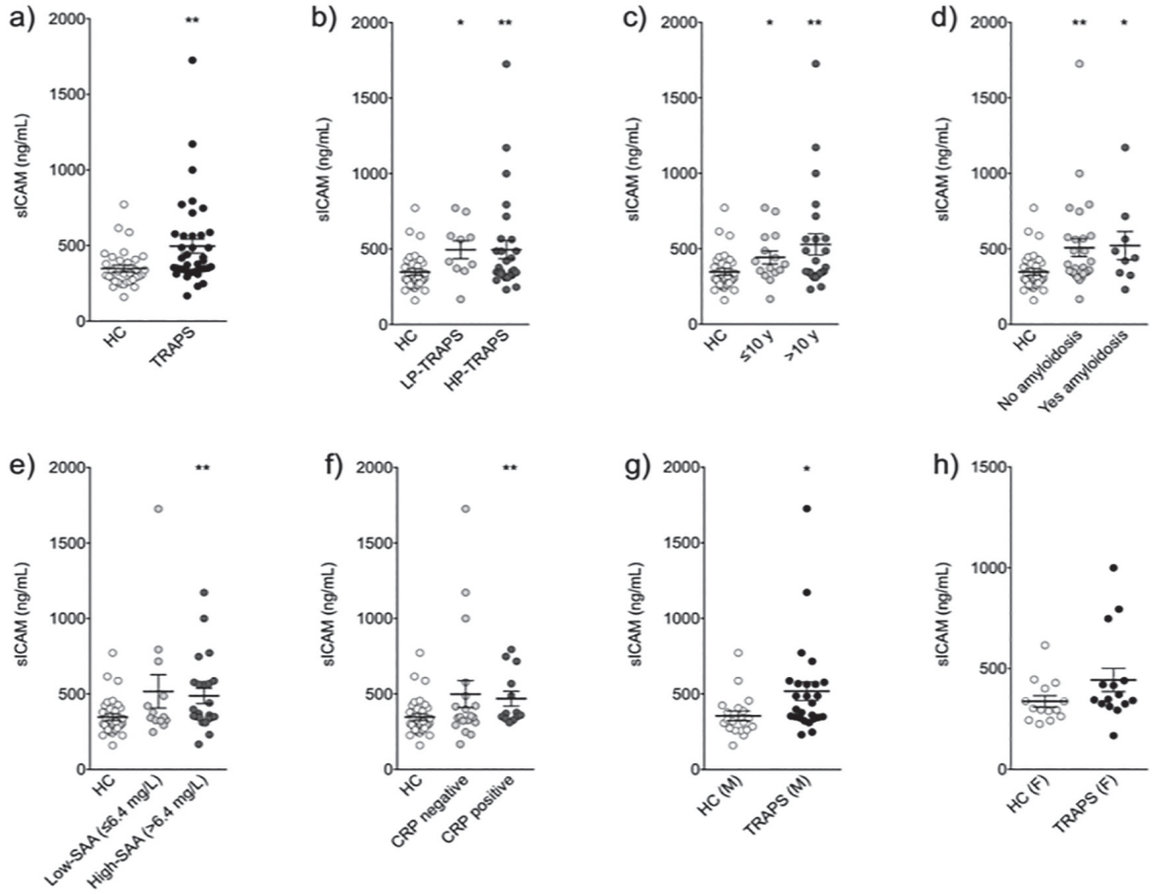

Fig. 1. shows the more relevant findings described in the present work, in particular the difference in sICAM levels between healthy controls (HC) and: TRAPS patients as a whole (a); patients carrying high-penetrance mutations and low-penetrance variants (b); patients with a less than 10 years and more than 10 years disease duration (c); patients with and without amyloidosis (d); patients with normal serum amyloid A (SAA) levels and increased SAA levels (e); patients with normal C-reactive protein (CRP) and increased CRP (f). The difference between male TRAPS patients and male HC is represented in the graphic g, while the difference between female TRAPS patients and female HC is represented in the graphic h. For comparisons between 2 groups we used Mann-Whitney U test; for comparisons among 3 groups we used ANOVA or Kruskall-Wallis test (as required). For variables that reached global significance, pairwise comparisons were performed by using the Mann-Whitney U test followed by Bonferroni correction.Significance between groups *versus* the HC group: *p<0.05, **p<0.01.

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