Acquired Cold Urticaria and Autoinflammatory Diseases: Results of Molecular Investigations in a Tertiary Reference Center

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Background

Acquired cold urticaria (ACU) is a type of inducible urticaria characterized by the development of itchy wheals after cold exposure. A generalized urticarial-like skin rash triggered and/or exacerbated by cold exposure also represents a characteristic feature of certain autoinflammatory diseases (AIDs).

Objectives

To investigate the presence of variants on genes causing AIDs with urticarial-like skin rashes as the most prominent cutaneous feature (*NLRP3*, *NLRP12*, *NLRC4* and *PLCG2*) in patients clinically diagnosed with ACU, in order to look for susceptibility factors of the disease.

Methods

Patients with cold urticaria symptoms without evidence of underlying diseases associated with secondary ACU referred to our Department during 2015-2018 were included in the study. Patients' clinical, demographic and laboratory data were collected, and germline and somatic variants on the *NLRP3*, *NLRP12*, *NLRC4* and *PLCG2* genes were searched using the next generation sequencing technology.

Results

Fifty patients were included in the study (Table 1). The median (range) age at disease onset was 39 (5-79) years, and 34 (68.0%) patients were female. None of the 50 patients referred family history of similar symptoms. Fourteen (28.0%) patients were diagnosed with atypical ACU. Regarding genetic studies, a total of 7 patients (14.0%) carried 8 heterozygous germline variants with allelic frequencies lower than 1% in public databases in the following genes: *NLRP3* (n=1), *NLRP12* (n=3), *NLRC4* (n=1), *PLCG2* (n=3) (Table 2). According to the current guidelines, all of them were classified as "likely benign" except three of them, which were classified as "variants of uncertain significance". No pathogenic or likely pathogenic variants were detected in any of the patients. Furthermore, deep analysis of the targeted 4 gene panel did not identify any post-zygotic variant. There are several reasons that suggest that the genetic variants found in our study do not play a relevant role in these patients: good response to urticaria therapies, normal values of acute phase reactants during urticarial flares, absence of family history and presence of the same genetic variant found in the patients' healthy relatives.

Table 2: Summary of genetic characteristics from patients carrying germline variants with allelic frequencies lower than 1% in public databases (1000 Genomes Project, gnomAD).

Patient (nº)	Gene	Nucleotide exchange	Amino Acid Exchange	1000 Genomes Project (%; hom)	Genome Agreggation Database (%;hom)	CADD	Pathogenicity classification
1	*NLRC4*	c.2785G>T	p.Ala929Ser	0.30; 0	0.76; 9	5.770	Likely benign
2	*NLRP3* *PLCG2*	c.2336G>A c.3125G>C	p.Gly779Asp p.Ser1042Thr	0; 0 0.82; 1	0.002; 0 0.30; 14	21,3 15,82	VUS Likely benign
3	*NLRP12*	c.857C>T	p.Pro286Leu	0; 0	0.014; 0	19,76	VUS
4	*NLRP12*	c.910C>T	p.His304Tyr	0.22; 0	0.45; 4	22,9	Likely benign
5	*NLRP12*	c.2830C>A	p.Arg944Arg	0.28; 0	0.34; 3	0,613	Likely benign
6	*PLCG2*	c.1274T>G	p.Phe425Cys	0; 0	0.0008; 0	27,2	VUS
7	*PLCG2*	c.1565C>G	p.Pro522Arg	0.28; 0	0.51; 8	17,37	Likely benign

Abbreviations: CADD, combined annotation-dependent depletion; hom, homozygous; VUS, Variant of uncertain significance

Table 1: Clinical and demographic characteristics of the study population

	Total patients (n=50)
Patients carrying germline variants on AIDs genes, *n (%)*	7 (14.0)
Female sex, *n (%)*	34 (68.0)
Median age, *years (range)*	39 (5-79)
Median age at disease onset, *years (range)*	27 (1-74)
Atopy, *n (%)*	11 (22.0)
Family history of cold-urticaria symptoms, *n (%)*	0 (0)
Angioedema, *n (%)*	8 (16.0)
Recurrent sinopulmonary infections, *n (%)*	5 (10.0)
Associated autoimmune conditions, *n (%)*	2 (4)
Disease severity, *n (%)*	
I	11 (22.0)
II	27 (54.0)
III	12 (24.0)
Fever or other systemic symptoms, *n (%)*	8 (16.0)
Cold triggers, *n (%)*	
Water	46 (92.0)
Solids	24 (48.0)
Air	41 (82.0)
Median CsTT, *min (range)*	3 (1-5)
Median CTT, *ºC (range)*	14 (4-26)
Median total serum IgE, *kU/L (range)*	69.5 (5-4700)
Elevated inflammatory markers, *n (%)*	7 (14.0)
Disease control, *n (%)*	45 (90.0)
Median disease duration, *years (range)*	7 (1-26)

Conclusions

According to our results, isolated ACU is not related to post-zygotic or germline pathogenic variants on the *NLRP3*, *NLRP12*, *NLRC4* and *PLCG2* genes. The present study also highlights the importance of being careful in the interpretation of low-penetrance mutations in subjects without enough evidence to suspect an AID, in order to avoid false positive diagnoses and the consequent overtreatment, given the high frequency of healthy carriers.

References

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