Criteria for CAPS, is it all in the name?

This paper¹ describes an original work conducted by an International team of 16 recognised clinical experts in the field of autoinflammatory diseases. The aim of this consortium was to develop diagnostic criteria for cryopyrin-associated periodic syndrome (CAPS). They resulted in a model that indisputably is relevant to describe these rare and heterogeneous diseases among other autoinflammatory diseases. Their proposed CAPS diagnosis criteria are primarily clinical.

We would like to comment on the pathophysiological mechanism underlying 'CAPS'. The *NLRP3* gene encodes cryopyrin, the historical name of the NLRP3 protein, a key component of the NLRP3 inflammasome.² As clearly stated by the authors, 'cryopyrin-associated periodic syndrome' includes, by definition, a group of diseases associated with *NLRP3* mutations. Deriving from this concept, a 'non-CAPS autoinflammatory disease' would correspond to a disease caused by mutations/polymorphisms in one or several other gene(s). The consortium nevertheless concluded that 'most importantly', the model 'did not mandate evidence of a disease-causing *NLRP3* mutation'. Indeed, somatic mosaicism can be missed by conventional sequencing approaches.³ However, the proposed criteria cannot *stricto sensu* be restricted to CAPS as it is likely to encompass syndromes caused by mutations in autoinflammatory genes other than *NLRP3*. For example, familial cold autoinflammatory syndromes (FCAS) can result from a number of recently discovered genes. FCAS1 (online inheritance in men (OMIM) no. 120100) is the classical FCAS caused by mutations in *NLRP3*; FCAS2 (OMIM no. 611762, also known as NLRP12-associated periodic syndrome (NAPS12), NLRP12-associated periodic syndrome), FCAS3 (OMIM no. 614468, also known as PLCG2-associated antibody deficiency and immune dysregulation (PLAID), Phospholipase C Gamma 2 (PLCG2)-associated antibody deficiency and immune dysregulation) and FCAS4 (OMIM no. 616115, also known as AIFEC, autoinflammation with infantile enterocolitis or recurrent macrophage activation syndrome) are due to the mutations in *NLRP12*, *PLCG2* and *NLRP4*, respectively. The proposed criteria (raised inflammatory markers, urticaria-like rash and arthralgia) would perform well with these four FCAS, but only FCAS1 is a CAPS. The authors

fairly admitted that 'the number of CAPS cases and controls was limited and not all possible differential diagnoses of CAPS may have been included, potentially leading to an overestimation of the specificity of the proposed model'.

The issue of the disease name, reflecting either the main symptoms or the molecular mechanisms of the condition, has been raised many times in the autoinflammatory diseases community, and propositions for refined taxonomy will shortly emerge. The debate is not just semantic as differential therapeutic approaches can be taken according to the molecular defect in cause in the condition presented by the patient.

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