Syndrome of Undifferentiated Recurrent Fever

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Syndrome of undifferentiated recurrent fever (SURF) is a heterogeneous group of autoinflammatory diseases (AID) characterized by self-limiting episodes of systemic inflammation without a confirmed molecular diagnosis, not fulfilling the criteria for periodic fever, aphthous stomatitis, pharyngitis and adenopathy (PFAPA) syndrome.

autoinflammatory diseases NGS SURF FMF colchicine anakinra

1. Introduction

Syndrome of undifferentiated recurrent fever (SURF) is a heterogeneous group of autoinflammatory diseases (AID) characterized by self-limiting episodes of systemic inflammation without a confirmed molecular diagnosis. First defined by Broderick et al., [1] SURF is increasingly diagnosed in patients with recurrent fever after exclusion of the main hereditary recurrent fevers (HRF) and periodic fever, aphthous stomatitis, pharyngitis and adenopathy (PFAPA) syndrome [2]. Recent evidence suggests the presence of a multi-organ presentation in SURF and, in a relevant percentage of the patients, a complete or at least partial response to colchicine, usually not observed with the same high frequency in PFAPA syndrome [3]. It is possible that omics-based technologies will provide a relevant opportunity to analyse the functional characteristics of immune cells in SURF patients, highlighting the pathological relevance of possible novel genes and supporting the development of new diagnostic tests. On the other hand, the response to colchicine suggests a possible crucial role of cytoskeleton and related proteins, as observed in the other form of HRF responding to this drug, namely the familial Mediterranean fever (FMF) [4].

2. Research progress

Inflammation is the first sign of immune system activation against pathogens and damage associated molecular patterns (DAMPS) in living organisms. In the case of the occurrence of inborn errors of immunity, the so-called *horror autoinflammaticus* may develop [5]. In the first conditions reported, the most characteristic clinical feature associated with AID was the recurrence of self-resolving fever attacks, namely HFR. However, a subclinical inflammation in affected patients may be associated with long term or life-threatening complications, such as amyloidosis, with an evident impact on quality of life and life expectation. An early diagnosis and a proper treatment may prevent a severe outcome.

Despite the fact that recurrence was implicit in the definition of the original group of HRF (FMF, MKD, TRAPS), the pathogenic mechanisms correlated with the alternation between flares of inflammation and periods of complete wellbeing still represent a dilemma. The existence is hypothesized of an unbalanced up-regulation of the

inflammatory response to common hits, followed by a negative feedback able to down-modulate the primary cause of the immune system hyperactivation. This virtuous cycle prevents an early exitus in people with minor defects in the innate immune system that can cause milder AID phenotypes and allows these mutations to be inherited across future generations. The molecular definition of numerous monogenic AID during the last 20 years dramatically increased our knowledge of the pathways and proteins involved in the innate immune system [6]. However, the large amount of patients displaying undefined recurrent fevers even after NGS suggests a need for further discoveries in the field.

In this review, we define a subset of undefined AID patients with recurrent inflammatory attacks and systemic manifestations not fulfilling the typical features of PFAPA syndrome, that represents an homogeneous subgroup of patients with recurrent fevers characterized by the classical triad of pharyngitis, cervical lymph nodes enlargement and aphthosis [7]. Fever is the physiological reaction to an increased concentration of inflammatory cytokines in the blood during an inflammatory response. This systemic inflammation often requires systemic drugs, such as specific cytokine blockers or other therapies able to prevent the unbalanced inflammatory response.

Among these drugs, colchicine is an ancient and well known agent. Colchicine acts as a cytoskeleton stabilizer with an evident efficacy in some HRF, namely FMF [8]. A similar effect has been shown in the present review in the majority of SURF patients treated with this drug [9]. The clinical definition of SURF as a well-defined and homogeneous clinical entity may be useful to further investigate the molecular basis of the role of the cytoskeleton in the activation and regulation of the inflammatory response. Furthermore, future studies may delineate novel treatments able to control the clinical manifestations of SURF.

This literature review has a number of limitations. First, the variability of the inclusion criteria used in the different analysed studies is associated with a relevant heterogeneity of the studied populations. Notably, in some studies, the exclusion of non-autoinflammatory syndrome was not formally specified. Finally, the not-homogeneous distribution of genes included in the different NGS panels cannot exclude that some patients could harbour mutations of some genes related to AID not covered by the panel used for that study. It is worth noting, however, that in all the analysed studies, the NGS panel included at least the four genes most frequently associated with HRF, namely MEFV, MVK, TNFRSF1A and NLRP3.

In conclusion, we reviewed the literature data regarding an emerging group of patients with recurrent fevers distinct from HRF and PFAPA syndrome, now defined as SURF. According to the analysis of the literature, a set of the clinical variables that could help to distinguish SURF from PFAPA and HRF can be empirically proposed (Table 3). A proper statistical analysis comparing a homogeneous group of SURF patients with patients with HRF and PFAPA will allow the creation of evidence-based classification criteria for SURF, with the final aim of favoring the harmonization of future studies in the fascinating field of AID still without a precise clinical and molecular characterization.

Table 3. Proposed empirical indications for the clinical suspicion of SURF.

Mandatory features
Recurrent fever with elevated inflammatory markers [1]
Negative criteria for PFAPA [2]
Negative genotype for HRF [3]
Additional supporting features
Monthly attacks
Attacks duration of 3–5 days
Fatigue/malaise
Arthralgia/myalgia
Abdominal pain
Eye manifestations [4]
Continuous colchicine/anti-IL1 response [5]

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