Editorial

Can we make a diagnosis of autoinflammatory diseases based upon clinical features only?

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Familial Mediterranean fever, which primarily affects the populations in Middle Eastern countries, is the first hereditary fever syndrome that has been genetically described (1). This was followed by tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS), previously named as Hibernian fever, where mutations in the *TNFRSF1A* gene were identified as the cause of this syndrome (2). It was only then that the term "autoinflammatory diseases" (AIDs) was proposed to define disorders characterised by recurrent or continuous inflammation due to defect(s) of the innate immune system, with no primary involvement of the adaptive immune system. Subsequently, hyperimmunoglobulinaemia D (HIDS), due to mutations in the *MVK* gene and cryopyrin associated periodic fever syndrome (CAPS) due to mutations in the *NLRP3* gene were described in patients with European and North American descent and were included into the list of AIDs (3, 4). Each of these conditions, however heterogeneous with regard to their pathogenesis, do share a clinical pattern manifested by 'seemingly unprovoked episodes of sterile inflammation' (5).

Some of the AIDs are more frequent in one population and in one part of the world than the others. That is why each one was initially described in the population with the highest prevalence. Thus, the ethnic background of the patient plays an important role in making a diagnosis and sometimes it takes time to recognise an AID in population where the disorder is rare. This has in fact happened in FMF, being for long time restricted only to the people of the Mediterranean basin; we now know, however, that it can also be seen in many other populations, including the Japanese (6).

FMF is characterised by recurrent attacks of fever and serositis lasting from 24–96 hours and resolve spontaneously (7). In Middle Eastern countries where FMF is prevalent, its diagnosis can be made based upon clinical ground only. However, genetic testing is generally required for the diagnosis of atypical cases, where patients develop late onset disease or lack typical FMF manifestations or present with atypical features. Moreover, in patients resembling other periodic fever syndromes or in patients with secondary amyloidosis with no known cause, genetic testing may also be of value. In some of these atypical presentations one can also use colchicine therapeutic test as an ad for FMF diagnosis.

The questions raised are whether we can apply the same approach to other AIDs and mainly among the so called "monogenic periodic fever syndromes": TRAPS, CAPS, MKD and the non-hereditary disease PFAPA (Periodic Fever, oral Aphthosis, Pharyngitis and cervical Adenitis) (8)? Can we make a diagnosis based upon clinical ground alone? Should we use genetic testing only in atypical presentations of AIDs? Do we have a therapeutic trial for diagnosis, as the case with colchicine in FMF?

Whatever the mutation and pathway involved, the common denominator of many AIDs is the excess of IL-1 production which characterises the expression of these diseases (9, 10). This may explain why many of these syndromes share some common features like self-limited attacks, fever, abdominal and/or chest pain, short-lived arthritis, erythematous rash and amyloidosis. On the other hand each has a list of more specific signs and symptoms that help in differential diagnosis. For example; in TRAPS; migratory and

tender rash, pericarditis, periorbital edema, conjunctivitis and attack duration of 7–21 days are almost unique to this syndrome (2). In MKD, aphthous stomatitis, enlarged and tender cervical lymph nodes and vaccination as a trigger of attack are also quite specific (3). In CAPS; urticarial rash, hearing loss, uveitis, aseptic meningitis, mental retardation and joint contractures are considered unique too (4).

The relatively common clinical features of AIDs make – sometimes – a clinical diagnosis of these disorders quite difficult. Moreover, the major problem in relying upon clinical features in making diagnosis of AIDs is the fact that the same genotype may display a totally different phenotype. For example, carriage of E148Q- P369S- R408Q mutations in the *MEFV* gene (in Cis) was responsible for livedoid vasculitis in a patient without any feature of FMF at all (11). S242R mutation in the *MEFV* gene was found to be associated with a disease called pyrin associated autoinflammation with neutrophilic dermatosis (PAAND) (12). In contrast to FMF, this disease is transmitted in autosomal dominant trait. Furthermore, the therapeutic approach is also different since this syndrome does not respond to colchicine and requires anti IL-1 agents.

In the current issue of this journal there are several interesting case reports which further illustrate rather unrecognised problems in diagnosing AIDs like the resemblance of a well-defined AID, to the most prevalent AID in that specific population.

Karacan *et al*. report four patients from 2 separate Turkish families with a clinical diagnosis of FMF but who are negative for *MEFV* mutations (13).

They describe a father and a daughter with recurrent, short-lived episodes of fever and abdominal pain complicated with AA amyloidosis that carry two heterozygous missense variants in TNFRSF1A. In the other family, total exome sequencing disclosed homozygosity of *MVK* mutations in the two siblings who presented with typical recurrent attacks of serositis, fever and red arthritis. These diagnoses are quite unexpected in a country like Turkey, where the prevalence of FMF is lying somewhere between 1–8/1000 of the general population.

On the other hand, a case report from Japan, may exemplify the opposite situation. A patient presenting with typical clinical features of chronic recurrent multifocal osteomyelitis (CRMO) and with no feature of FMF, was tested genetically and found to carry 3 *MEFV* mutations (E148Q-P369S-R408Q) in Cis (14). Thorough search for mutations in LPIN2 or in other genes of AIDs failed to show any additional genetic finding. Here again *MEFV*-related genotype displays totally different clinical manifestations than FMF.

These reports raise again the question of diagnosis based upon clinical features. In all the above reported cases relying upon the clinical manifestations without performing genetic analysis would probably lead us to erroneous diagnoses.

An additional issue to be discussed is whether we can make a diagnosis of a disease transferred as autosomal recessive trait in a patient who carries a single mutation only (heterozygote)? We know that in FMF, about one third of the patients carry only a single *MEFV* mutation. Nevertheless, about 98% of individuals carrying a single *MEFV* mutation are asymptomatic. In fact, a single abstract describing several cases of symptomatic HIDS (MKD) who were heterozygotes has been reported (15). However, the authors admit that they did not make further efforts in order to detect other rare mutations (personal communication). Moreover, since mutations in *MVK* are associated with loss of gene function, the normal allele is usually capable of replacing this loss and therefore these individuals are not symptomatic. Thus, in contrast to FMF, we cannot make a general statement saying that AIDs transmitted as autosomal recessive trait may present clinically despite carrying a single mutation.

Some reports claim that 5–10% of FMF patients do not carry the *MEFV* mutation (2). The cases described by Karacan et al. show that these patients with typical FMF features did not carry any *MEFV* mutation while being homozygotes for *MVK* mutation or carriers of two heterozygous missense variants in TNFRSF1A. These observations pose a serious question as to our capability to make a diagnosis of AIDs in patients who do not carry any mutation. In this respect, one may raise a question whether there is FMF or any other AIDs with no *MEFV* mutations or other corresponding gene mutations, respectively. The above examples show that the phenotype does not always reflects the exact genotype. These examples emphasise the significance of genetic analysis in making the diagnosis of the autoinflammatory diseases.

The question then is: can we make a diagnosis based upon genetic testing only? The answer is generally yes. In cases where the clinical features are typical for an AIDs and the genetic testing is that of a different AID the diagnosis will be dictated by the genetic findings while mentioning that it is an unusual presentation of these mutations. However, genetic testing is not always the absolute solution for diagnosis. For example, a few years ago, a patient with recurrent attacks of fever, arthralgia, skin rash and angioedema came to an FMF clinic. Genetic test disclosed that the patient carried two *MEFV* mutations (A726V and E148Q) and therefore a diagnosis of FMF was made and colchicine treatment was initiated. Due to lack of response, the patient came to our clinic where we realised that his father had similar symptoms. Genetic testing of his parents showed that his symptomatic father did not carry any *MEFV* mutation while his asymptomatic mother carried both mutations in Cis. This is thus an example where the genetic analysis led to an erroneous diagnosis of FMF.

Do we have additional measures to make a diagnosis in recurrent fever syndromes, apart from the clinical features and the genetic testing?

In cases of suspected FMF (carriage of a single mutation, lack of any known *MEFV* sequence variant, atypical clinical presentation), we do have a colchicine therapeutic test which can be used to confirm the diagnosis. Can we do the same for diagnosing other AIDs?

Theoretically, anti-IL-1 agents could serve as therapeutic trial for diagnosis

of AIDs. However, it seems that this approach is not applicable in the current cases, since all these diseases may respond to anti IL-1 medications.

So, what are the lessons to be learned from the above observations?

1. Clinical features of AIDs are not always specific!!
2. Genetic results are not always definitive!!

We have to use our experience and clinical skills and to consider the weight of the clinical features, their specificity for the appropriate AID and the genetic results, where available.

When the clinical features allude to a specific AID which is confirmed by unequivocal genetic results, the diagnosis is then definite.

When the clinical features are typical for a specific disease, but no mutation is found following thorough genetic analysis, we should rely on the clinical presentation only and the diagnosis will be probable.

When the clinical features do not meet the genetic results and the genetic results are unequivocal (mutations known to cause the disease), the diagnosis should be dictated by the genetic findings. In these cases we have to mention the "atypical" features within the diagnosis. For example, in the case reported where genetic analysis showed *MVK* mutations but the clinical features were those of FMF (serositis), the appropriate name would be "MKD with serositis".

When the clinical features are not specific for a unique AID and there is no unequivocal genetic finding, a diagnosis of "undefined AID" should be used. In these cases we have to search for new diseases or to follow the patients and to see whether they will add more criteria for a more accurate diagnosis later, since in many diseases the clinical features gradually appear over time. Using the terms "probable" diagnosis or "undefined AID" does not preclude, by all means, the right of the treating physician to start treatment based upon his clinical judgement. In most of the above mentioned AIDs a therapeutic trial with colchicine or anti IL-1 agents (canakinumab, rilonacept and anakinra) may be justified, even in the absence of confirmatory genetic tests (13).

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