IMMUNOSENESCENCE AND LATE-ONSET FAMILIAL MEDITERRANEAN FEVER

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Abstract
Familial Mediterranean fever (FMF) is an autoinflammatory disease that causes recurrent fever and serositis. FMF often begins in childhood and is diagnosed at an early age. Although it is uncommon for the disease to occur after the age of 40, late-onset patient series have been published and compared to early-onset patient series in recent years. Although it is a genetically inherited disease, the reason why clinical symptoms appear at such a late age in some patients is unknown. The frequency of pathogenic mutations is lower in these patients than in early-onset FMF patients, and the disease has a milder course. Whether or not this clinical presentation is related to immune system changes associated with aging is an open question. Age-related immune system changes, such as an increase in senescence cells, the development of senescence-associated secretory phenotype, and a decline in autophagy with age, can trigger the inflammasome activation. In this regard, understanding the cause of the late-onset of FMF attacks may open up new avenues for research into pathogenesis.
In this review, we will first compare the clinical features of the early and late-onset FMF series. We will then consider hypothetical causes of late-onset FMF attacks by reviewing age-related changes in the innate immune system.

Keywords: Familial Mediterranean Fever, Late-onset, Aging, Immunosenescence

Introduction
Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease characterized by recurrent, short-term inflammatory attacks that resolve spontaneously within 1-3 days. FMF is common among people in the eastern Mediterranean region, including the Jewish, Turkish, Armenian, and Arab populations. The prevalence of FMF in these ethnic groups is between 1/500 and 1/1000. FMF usually begins in childhood.

In a multicenter study, the mean age of onset was reported as 9.6 years [1]. The most well-known clinical manifestations of FMF are episodes of serositis and fever, including abdominal pain and chest pain. The most important and prognostic complication of the disease is amyloidosis [2]. Autoinflammatory diseases are associated with abnormal activation of the innate immune system, resulting in clinical inflammation and high levels of acute-phase reactants. FMF is a disease caused by
the Mediterranean fever (MEFV) gene, which codes for the pyrin protein. It is known that the MEFV gene is located on the short arm of the 16th chromosome and encodes a cytoplasmic protein of 781 amino acids called pyrin/marenostrin, which exists in mature neutrophils and monocytes together with microtubules. Pyrin regulates interleukin (IL)-1β activation and inhibits nuclear factor-kB (NF-kB) activation and apoptosis [1,3].

90% of FMF patients have their first attack before the age of 20. The disease rarely manifests itself after the age of 40 [1]. In recent years, late-onset FMF series have been published. Despite having similar genetic characteristics, it is unknown why attacks occur at a later age. Aging is a complicated process that affects immune cells. Although there is no information or publication about the clinical and cellular effects of aging on FMF, it may be possible to make some assumptions by taking advantage of immune system changes that occur with age.

In this review, we will focus on the possible role of cellular and metabolic changes in the immune system that occur with age in the emergence of late-onset FMF. For this, we will first discuss the pathogenesis of FMF. Subsequently, the changes in innate immunity that occur with age will be revealed and their possible roles in the emergence of FMF attacks will be discussed.

Search Strategy

We searched the databases of Scopus, MEDLINE/PubMed and Web of science using the keywords “Familial Mediterranean fever (FMF)” [AND] “late-onset” [OR] “pediatric-onset” [OR] “aging” [OR] “immunosenescence”. Original research articles and review articles which written in English were selected for the study. Case reports were excluded. Articles on immune aging were searched using the keywords “immunosenescence” [OR] “aging”.

Discussion

Pathogenesis of Familial Mediterranean Fever

The innate immune system is vital in host defense against pathogens entering the body. Pattern-recognition receptors (PRRs) are very important in the innate immune response. They recognize the exogenous pathogen-associated molecular pattern (PAMPs) and the endogenous injury-associated molecular pattern (DAMPs) and initiate signaling pathways that regulate the transcription of proinflammatory cytokines, mainly through NF-kB and interferon regulatory factors. An important class of PRR is the NOD-like receptor (NLR) family. NLRP3 inflammasome, one of the NLR molecules, is a multimeric protein complex. Various danger signals such as DAMPs or PAMPs are required for NLRP3 inflammasome activation to occur. In response to these stimuli, caspase-1 is activated. Activation of caspase 1 leads to the production of active IL-1β, a potent proinflammatory cytokine [1].

FMF is a disease caused by the MEFV gene, which codes for the pyrin protein. Although the exact function of the pyrin protein is unknown, it is thought to be a "gain-of-function with a gene dosage effect [4]. The regulation of pyrin is linked to host Ras homologous protein guanosine triphosphate (Rho GTPase) activity. Pyrin is indirectly affected by factors that modify GTPase RhoA activity, without directly interacting with these factors. PKN1 and PKN2 are Ras's homolog family member A (RhoA)- dependent serine/threonine-protein kinases that phosphorylate pyrin at Ser208 and Ser242. This cause pyrin to come into contact with the chaperone proteins 143-3e and 14-3-3s. This interaction keeps pyrin dormant and prevents the formation of an active inflammasome. RhoA inactivation decreases PKN1 and PKN2 activity, resulting in lower levels of phosphorylated pyrin. This, in turn, frees pyrin from the inhibitory 14-3-3 proteins, hastening the formation of an active pyrin inflammasome [5]. When the inflammasome forms, caspase-1 autocatalytically activates, cleaving the pro-enzyme into the active subunits. The active enzyme forms heterodimers and causes the release of mature IL-1β/IL-18. In addition to the clostridial toxin, bacteria and/or toxins such as pertussis toxin (Bordetella pertussis), VopS (Vibrio parahaemolyticus), IbP (Histophilus somni) are responsible for GTPase RhoA modification [6-8]. In addition, catecholamines, which are stress mediators, can also make RhoA modifications by increasing the level of cyclic adenosine monophosphate (cAMP) in innate immune cells [9]. Catecholamine-induced Rhoa modification may aid in understanding why FMF attacks occur following stress exposure. Physical...
and emotional stressors are well known to trigger FMF attacks, and in clinical practice, increased colchicine dosing is used during these times [10].

Neutrophils are the most important cells in the pathogenesis of FMF. Neutrophil extracellular traps (NETs) are also effective in the pathogenesis of FMF [11-13]. It has been shown that FMF attack is characterized by the release of NETs containing active IL-1β. These NETs structures are observed in the first hours of FMF attacks and decrease as the inflammatory attack resolves. It has been suggested that NETs down-regulate more NETs and accelerate the resolution of attacks. Since NET formation requires induction of autophagy, it has been suggested that reduced basal levels of autophagy in these cells may protect them from attacks by reducing the release of pro-inflammatory NETs [13].

**Aging and Innate Immune System Changes**

With age, the immune system can undergo remodeling. Many complex life events influence the immune system's remodeling process, which affects both innate and adaptive immunity. Monocytes and macrophages are the most important cells of innate immunity. There may be variability in Toll-like receptor (TLR) expression and signal activity of dendritic cells and monocytes with age. With increasing age, a decrease in TLR level and the signal response of dendritic cells (DC) is observed [14]. For instance, NF-kB activation in response to the TLR5 signal can be incomplete [15]. Older people's ability to respond to TLR4 and TLR7/8 agonists is much slower than the younger age group [16].

Neutrophils' microbicidal activity declines with age. This is due to neutrophils' impaired phagocytosis, degranulation, and ROS production [17-20]. The NET formation also decreases with age. This is a result of the increased release of neutrophil elastase during degranulation [21]. On the other hand, innate immunity cytokines such as IL-6, tumor necrosis factor (TNF)-alpha, and IL-1beta increase with age [22]. This has been demonstrated in both in vitro stimulated peripheral mononuclear cells and blood measurements taken from elderly patients [23-25]. Interestingly, while pro-inflammatory cytokines increase with age, an increase in anti-inflammatory cytokines accompanies this [26]. The phenotype and functions of natural killer (NK) cells can also change with age [27]. Activation of NK cells is expected to increase due to the increased DAMP concentration.

However, as a result of senescence, their proliferative capacity and functional properties decrease [28,29].

Aging also causes metabolic dysregulation. Metabolic dysregulation occurs at both the systemic and cellular levels [30]. According to new research, senescence cells accumulate with age. Senescent cells are considered important contributors to the pro-inflammatory phenotype [31]. Although senescence cells cannot proliferate, they can produce a Senescence- Associated Secretory Products (SASPs) [32]. These include cytokines like IL-1, IL-6, TNF-alpha, chemokines, and other molecules. These factors change tissue microenvironments, resulting in chronic, basal, and sterile inflammation, also known as inflammaging [32,33]. SASPs produced by senescence cells act like DAMP, activating NF-kB via NLRP3 inflammasome stimulation. Age-related decreases in autophagy also play a role in this process. Although aging macrophages' ability to present antigen and perform phagocytosis is reduced, inflammatory pathways in aged macrophages, including the NLRP3 inflammasome, are activated.

Immunometabolism is the name given to immune cell metabolism, and it is regarded as the most important modifier in immune cells. Nicotinamide Adenine Dinucleotide (NAD), which is synthesized de novo in macrophages, regulates mitochondrial function, macrophage phenotype, and inflammation [34,35]. However, NAD deficiency occurs in aging macrophages as a result of the SASP effect, which causes inflammasome activation and inflammation [31,32,36].

As a result, the increase in senescence cells, an increase in SASPs, and a decrease in age-related autophagy, depending on the metabolic changes caused by age, lead to an inflammatory microenvironment and inflammasome activation.

**Clinical Features of Familial Mediterranean Fever by Age and Late-onset Familial Mediterranean Fever**

Approximately 90% of FMF patients experience their first attack before the age of 20 (37). FMF with the first attack at age ≥ 40 years is rare and there are only a few studies investigating the clinical and molecular genetic characteristics of late-onset FMF patients [38-40]. There is no definitively accepted
age limit for late-onset FMF disease. In some studies, this limit is >20 years old, while in others it is ≥40 years old (38-41). Tamir et al examined FMF patients whose attacks of FMF started after the age of 40 and showed that they had a milder disease course. They also found that M694V homozygosity was less than the control group. They suggested that environmental, physical, and mental factors are not responsible for the late-onset attacks of FMF patients [42].

There is no data in the literature that clinical findings and disease activation decrease with age in the course of FMF. However, there is limited information about clinical findings, genetic findings, and activation in late-onset FMF patients. In a study that included Armenian patients aged ≥40 years at the first attack, 354 (3.4%) late-onset FMF cases were found among 10370 FMF patients. A milder disease phenotype, including less frequent fever, skin manifestations, and chest pain was detected in patients with late-onset FMF [39].

In another study from Turkey, which aimed to compare patients aged≥40 years at first attack with early-onset patients in terms of clinical and genetic characteristics, late-onset was found in 41 (2.02%) patients out of 2020. Similarly, a lower frequency of fever, lower daily colchicine dose, and a lower prevalence of exon 10 mutations and a milder disease were found in this study [38] (Demographic and clinical characteristics of pediatric-, classical-, and late-onset FMF patients are given in Table 1).

The Possible Role of Immunosenescence in the Late-onset Familial Mediterranean Fever Attacks

There is no research on immunosenescence in FMF patients. We assume the possible mechanism of late-onset FMF by exploiting age-induced innate immunity changes. As previously stated, attacks occur at a later age in a small proportion of patients with FMF. Tamir et al suggested that environmental, mental, and physical factors are not responsible for late-onset of FMF attacks, but genetic factors may be responsible [42]. Having less pathogenic mutations may be associated with a milder phenotype rather than a later onset of attacks. Other factors must play a role in its later emergence. As well known, FMF mutations in pyrin lower the activation threshold of the pyrin inflammasome. A self-limited inflammatory attack develops in FMF patients only when the inflammatory pathway is activated by an insult, which is consistent with the "hyperinflammatory" state [45]. Regulation of innate immunity depends on triggers that stimulate innate cell sensors and negative regulators. Disruption of this balance leads to inflammasome activation and the formation of inflammation. So why do attacks occur at a later age, in contrast to most patients, in a minority of patients despite having the MEFV gene mutation?

This may be related to the fact that the endogenous or exogenous stimulus required for the occurrence of an attack does not exceed the threshold value required for the attack in the late-onset FMF patients. However, inflammatory microenvironment and inflammasome activation due to immuno-metabolic changes and immunosenescence appearing with age may contribute to the emergence of attacks by creating an additional inflammatory stimulus.

At this point, a question may come to mind. Can these age-related changes increase the severity and the frequency of attacks in patients with early-onset FMF? So far, neither the literature nor our clinical experience contains such information. There is no recommendation for increasing the dose of colchicine in FMF patients who are getting older. The reason for this may be related to the fact that the immune system does not show a linear behavior. Due to its plasticity feature the immune system also develops anti-inflammatory mechanisms against inflammation and may lead to long-term suppression of inflammation [46]. These conditions, which are considered the burn-out of the inflammatory disease, may develop in the course of inflammatory diseases [47]. In these processes, immunosenescence can also create a desirable situation because it reduces the inflammatory response. In other words, immunosenescence can suppress both the inflammatory tendency and the inflammatory response with accompanying mechanisms because it can trigger an anti-inflammatory response to counteract the pro-inflammatory environment [48]. In this process, the individual's immunobiography is very important.

Conclusions

As a result, immunosenescence may cause attacks in a smaller proportion of patients with FMF later in life. Cellular studies in patients with early-onset and
late-onset FMF will provide important information about the role of aging in the disease's pathogenesis.

Table 1. Demographics and clinical characteristics of pediatric-, classical-, and late-onset Familial Mediterranean Fever patients

<table>
<thead>
<tr>
<th></th>
<th>Pediatric FMF</th>
<th>Classical FMF</th>
<th>Late onset FMF (≥40 years)</th>
<th>Late onset FMF (≥40 years)</th>
<th>Late onset FMF (≥40 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>3454</td>
<td>2246</td>
<td>20</td>
<td>41</td>
<td>354</td>
</tr>
<tr>
<td>Frequency of late onset FMF</td>
<td>-</td>
<td>-</td>
<td>0.5%</td>
<td>2.02%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Country</td>
<td>Turkey</td>
<td>Turkey</td>
<td>Israel</td>
<td>Turkey</td>
<td>Armenia</td>
</tr>
<tr>
<td>Age, mean±SD, yrs</td>
<td>12±5.2</td>
<td>34.5± 11.9</td>
<td>60.3±9.1</td>
<td>57.6 ± 6.72</td>
<td>56.97±7.82</td>
</tr>
<tr>
<td>Age at symptom onset, mean±SD, yrs</td>
<td>5.1±3.8</td>
<td>15.7 ± 9.6</td>
<td>44.5±4.3</td>
<td>44.7 ± 4.86</td>
<td>46.02±5.57</td>
</tr>
<tr>
<td>Age at diagnosis, mean±SD, yrs</td>
<td>7.3±4</td>
<td>25.8 ± 11.6</td>
<td>49.4±5.7</td>
<td>50.3 ± 6.72</td>
<td>-</td>
</tr>
<tr>
<td>Delay in diagnosis, mean±SD, yrs</td>
<td>15 months (median)</td>
<td>10.1 ± 9.9 yrs</td>
<td>4.9±5.8 yrs</td>
<td>5.6 ± 5.75 yrs</td>
<td>-</td>
</tr>
<tr>
<td>Gender, Male/Female</td>
<td>1699/1755</td>
<td>1049/1197</td>
<td>16/4</td>
<td>Female to male ratio 1.7/1</td>
<td>160/194</td>
</tr>
<tr>
<td>Clinical findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>86.7%</td>
<td>91.9%</td>
<td>5%</td>
<td>63.4%</td>
<td>89.5%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>88.2%</td>
<td>94.6%</td>
<td>100%</td>
<td>87.8%</td>
<td>90.4%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>20.2%</td>
<td>47.6%</td>
<td>5%</td>
<td>14.6%</td>
<td>43.2%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>27.7%</td>
<td>39.8%</td>
<td>10%</td>
<td>24.4%</td>
<td>17.5%</td>
</tr>
</tbody>
</table>

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REFERENCES


