
Musculoskeletal manifestations in hereditary periodic fever syndromes

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ABSTRACT

Monogenic autoinflammatory diseases (AIDs) are a group of inflammatory disorders induced by deregulation of the innate immune system and characterised by inflammatory bouts with fever as well as a large spectrum of other possible manifestations involving most organs and tissues. In this context, musculoskeletal manifestations represent a frequent finding in the clinical picture of patients with AIDs and may range from less severe affections including myalgia and arthralgia to severe arthritis, muscle fasciitis, bone erosions, and joint deformities. Therefore, as diagnostic suspicions originates from a careful and detailed clinical evaluation, physicians dealing with monogenic AIDs should bear in mind their possible muscle and joint manifestations, some of which are typical and very useful for diagnostic purposes. Indeed, their prompt recognition may reduce the diagnostic delay thus allowing an early and appropriate therapeutic management. For these reasons, the present review is aimed at providing a wide overview on the different patterns of joint and muscle affections in the four main monogenic AIDs.

Introduction

Monogenic autoinflammatory diseases (AIDs) are a relatively new group of inflammatory disorders caused by mutations in genes encoding for proteins involved in the regulation of the innate immune system (1). The most frequent and well-defined AIDs are: familial Mediterranean fever (FMF), an autosomal recessive condition caused by mutations in the Mediterranean FeVer (MEFV) gene that codes for the pyrin protein, which modulates inflammation and apoptosis through regulation of intracellular activation of interleukin (IL)-1 β and IL-18; cryopyrin-associated periodic syndromes (CAPS),

a group of three AIDs associated with mutations in the NATCHT, LRR and PYD domains-containing protein 3 (NLRP3) gene, which encodes for cryopyrin, a component of the inflammasome; tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), an autosomal dominant disease related to missense mutations in the TNFRSF1A gene, that encodes for the TNF receptor 1; and, mevalonate kinase deficiency (MKD), a second autosomal recessive disease caused by a loss of function of the mevalonate kinase (MVK) enzyme, involved in the cholesterol biosynthesis pathway (2-5). From a clinical point of view, monogenic AIDs are characterised by recurrent fever episodes variously accompanied by systemic and/or organ-specific inflammation potentially affecting all organs and tissues (6-10). In this regard, Table I provides a summary overview on the genetic and clinical features which characterise the main four monogenic AIDs.

The last decade has witnessed considerable changes regarding monogenic AIDs in terms of diagnostic approach, treatment, and prognosis (11-15). In particular, AIDs are no longer purely a matter for paediatricians, with the possible onset of symptoms during adulthood now well established. However, a delayed presentation is generally associated with low-penetrance mutations and more often manifests with oligo-symptomatic course and/or atypical presentation (16-20). Consequently, a careful and detailed clinical assessment of signs and symptoms is mandatory to early identify patients with monogenic AIDs, especially in cases with no textbook presentation. Essentially, a diagnosis is typically based on clinical assessment and, when required, genetic analysis, and should be driven by the clinical features of patients (11, 17, 21). On this basis, physicians dealing with

Table I. Summary of the molecular, genetic and clinical features of the four main monogenic autoinflammatory diseases. (Note: musculoskeletal manifestations are described in Table II).

Disease	Gene Locus	Inheritance	Protein involved	Main clinical manifestations
FMF	MEFV 16p13.3	AR	Pyrin (or marenostrine)	Fever, serositis, erysipelas-like rash, amyloidosis in untreated patients
TRAPS	TNFRSF1A 12p13	AD	Tumour necrosis factor receptor 1	Fever, migrating erythematous skin rash, conjunctivitis, periorbital oedema, serosal involvement, amyloidosis
MKD	MVK 12q24	AR	Mevalonate kinase	Fever, polymorphous skin rash, abdominal pain, diarrhoea, lymph node enlargement, splenomegaly, aphthosis
MA	MVK 12q24	AR	Mevalonate kinase	Psychomotor retardation and growth delay, progressive cerebellar ataxia, dysmorphisms, vision deficits in addition to MKD symptoms
FCAS	NLRP3 1q44	AD	Cryopyrin	Fever, urticarial rash, conjunctivitis, headache
MWS	NLRP3 1q44	AD	Cryopyrin	Fever, urticarial rash, conjunctivitis, episcleritis, neurosensorial deafness, amyloidosis
CINCA/NOMID	NLRP3 1q44	AD	Cryopyrin	Fever, urticarial rash, uveitis, papilledema, chronic aseptic meningopathy, neurosensorial hearing loss, amyloidosis

AD: autosomal dominant; AR: autosomal recessive; CINCA: chronic infantile neurologic cutaneous and articular syndrome; FCAS: familial cold autoinflammatory syndrome; FMF: familial Mediterranean fever; MA: mevalonic aciduria; MEFV: MEiterranean FeVer; MKD: mevalonate kinase deficiency; MVK: mevalonate kinase; MWS: Muckle-Wells syndrome; NLRP3: NACHT, LRR and PYD domains-containing protein 3; NOMID: neonatal-onset multisystem inflammatory disease; TNFRSF1A: tumour necrosis factor receptor super family 1A; TRAPS: tumour necrosis factor receptor-associated periodic syndrome.

monogenic AIDs have to bear in mind the protean clinical presentations of patients complaining from such disorders. As musculoskeletal involvement often affects patients with AIDs, the present review is aimed at compiling an overview on the different patterns of joint and muscle affections in the four main monogenic AIDs.

Familial Mediterranean fever

Among AIDs, FMF is the most prevalent and is characterised by self-limiting recurrent episodes of fever frequently associated with polyserositis, predominantly manifesting as acute abdominal and chest pain. Together with serositis and fever, articular involvement is so typical of FMF that it is included in the diagnostic criteria for both children and adults (22, 23).

Acute attacks last 2 to 3 days and recovery is usually complete, with no sequelae despite recurring episodes of arthritis. It has been estimated that up to three quarters of patients with FMF experience acute articular attacks, often manifesting with pain and swelling of one joint at a time, especially the

large joints of the lower limbs. However, other articulations such as shoulder, temporomandibular or sternoclavicular joints, can also be involved (24-27).

It is noteworthy, that arthritis may be the sole manifestation of the disease in up to 15% of FMF patients (28, 29). Brik *et al.* surveyed 136 paediatric patients genetically diagnosed with FMF and found that acute episodes of monoarthritis occurred in 71% of Jewish children, who were all homozygous or compound heterozygous for the M694V mutation, while Arab children were less likely to develop monoarthritis (40%) and were genetically homozygous or compound heterozygous for any one of the five mutations tested (M694V, V726A, M680I, M694I, and E148Q) (30). Of note, monoarthritis was never found among patients not fulfilling the criteria for a clinical diagnosis of FMF (30). In addition, despite the typical monoarthritis found in FMF, Jarjour *et al.* recently reported the frequent identification of symmetrical arthritis simultaneously affecting two large joints of the lower limbs in 71 FMF patients (31).

Though less typical than acute arthritis, subacute or chronic articular involvement has been described in 5% of FMF individuals (27). Subacute arthritis is characterised by the sudden onset of either mono- or oligo-arthritis, mainly affecting the large lower limb joints. In these cases, pain and inflammation generally disappear within 2 weeks, though flexion contractures of involved joints may seldom occur (27, 32-34).

In contrast to the positive outcome of acute and subacute forms, chronic arthritis can affect knees and hips with destructive sequelae, often leading to early prosthetic joint replacement (35). Chronic involvement of the hip may follow either recurrent articular flares or a unique prolonged episode, potentially resulting in a severe deterioration of the articular cartilage or even in the aseptic necrosis of the femoral head (36-38). To avoid this last complication, Sohar *et al.* recommended repeated arthrocentesis of the hip in order to prevent compression-related ischaemia (39).

Of note, although knee and hip are more frequently involved in FMF, the

chronic form of arthritis may sometimes affect the joints of upper parts of the body, especially the elbow, sternoclavicular joints, and metacarpophalangeal joints (33, 40).

Besides peripheral arthritis, sacroiliitis is a common finding in FMF. The first mention of sacroiliac joint involvement in FMF patients dates back to 1963 (41). More recently, Akar *et al.* found an increased prevalence of spondyloarthritis and ankylosing spondylitis (AS) in a cohort of FMF patients, with FMF patients affected with AS negative for human leukocyte antigen (HLA)-B27 and more likely to carry the M694V mutation (42). In line with this study, other studies have highlighted the M694V in 69–80% of FMF patients with arthritis (43–45), while Tufan *et al.* identified a high prevalence of enthesopathy among FMF patients carrying the M694V mutation (46). However, the finding by Tufan *et al.* was not confirmed in a similar study by Yilmaz *et al.*, who did not identify a relationship between enthesopathy and the M694V mutation in FMF patients (47). As a summary of this data, Gülhan *et al.* suggested that *MEFV* mutations, especially M694V, may represent a susceptibility factor for enthesitis-related arthritis in populations of the Mediterranean basin (48). In this context, Esched *et al.* investigated 11 FMF patients presenting with exertional leg pain after minor exercise (49). Magnetic resonance imaging (MRI) showed signs of enthesopathy of the lower limb extremities in 10 out of 11 patients, while 8 out of 10 patients had signs of sacroiliitis with pelvic x-rays, suggesting that exertional leg pain in FMF patients could be included in the spectrum of spondyloarthropathies (49).

With regards to muscle symptoms, up to 25% of patients with FMF report myalgia, which may be spontaneous, induced by exercise, or part of a protracted febrile myalgia syndrome (PFMS) (50). The identification of myositis is an uncommon finding in FMF and was found to be IL-1 related (51).

Langevitz *et al.* initially described PFMS in 1994 in 14 FMF patients who showed a dramatic response to corticosteroids (52). Though extremely rare,

PFMS is mainly described in subjects carrying the M694V mutation (53). PFMS represents a severe manifestation characterised by debilitating febrile myalgia of the upper and lower extremities, possibly accompanied by other FMF symptoms such as abdominal pain, diarrhoea, arthritis/arthritis, and transient vasculitic purpura mimicking Henoch-Schönlein purpura. Inflammatory markers are increased, while creatine phosphokinase (CPK) levels are generally normal. Conversely, electromyography shows unspecific changes. When untreated, PFMS generally lasts from 4 to 6 weeks.

Finally, colchicine-induced myotoxicity (CIM) is a rare condition in patients with FMF (54, 55). It has been described both in cases with long-lasting colchicine treatment and in patients with a less than 1-month treatment course (56). Patients affected with CIM typically present a proximal muscle weakness, especially in the lower extremities; CPK levels are usually elevated and electromyography shows unspecific myopathic changes. Muscle biopsy may show vacuolar changes originating from lysosomes and owing to microtubule dysfunction in muscle cells (55). Symptoms of CIM regress and creatine kinase levels return to normal values within several days to weeks after discontinuing colchicine; however, any concomitant neuropathy may resolve more slowly.

Cryopyrin-associated periodic syndromes

CAPS are caused by gain-of-function mutations in the *NLRP3* gene, which takes part in the assembly of the NALP3-inflammasome. This multiprotein complex is involved in the cleavage of pro-IL-1 β into its bioactive form IL-1 β through caspase 1 activation (57, 58). The “CAPS spectrum” includes three different clinical phenotypes characterised by an increasing level of severity: familial cold-associated autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurologic cutaneous syndrome (CINCA), also known as neonatal-onset multisystem inflammatory disease (NOMID) (59). FCAS

is the mildest type and is characterised by fever, urticarial rash, asthenia, conjunctivitis, and intermittent arthralgia triggered by generalised cold exposure. Episodes are usually self-limiting and resolve within a few days (60). In addition to symptoms characterising FCAS, MWS manifests with arthritis and a progressive bilateral sensorineural hearing loss (61–63). CINCA/NOMID is the most severe form and presents with chronic urticarial rash, early central nervous system involvement with chronic aseptic meningitis, increased intracranial pressure, cerebral atrophy, ventriculomegaly, and chronic papilledema followed by optic-nerve atrophy and loss of vision. Mental retardation, seizures, and sensorineural hearing loss represent other possible challenging manifestations (59, 64, 65). Articular involvement in CAPS affects approximately 60% of all patients and ranges from arthralgia and transient joint swelling during flares to severe disabling joint disease (66). Patients with CINCA/NOMID show the most challenging joint manifestations with chronic arthritis and conspicuous structural changes in both epiphyses and growth plates of large joints, resulting in bony overgrowth and gross deformities. Knees are the most frequent joints involved in such patients (65). The chronic articular involvement of CINCA/NOMID classically begins during childhood, leaving the patient with skeletal deformities that result in degenerative arthropathy and joint contractures from early adulthood. In this regard, according to an Italian study describing both clinical and genetic features of 12 CINCA patients, inflammatory or deforming arthropathy was reported in 11 out of 12 patients and patellar premature ossification and overgrowth in 8 out of 12 patients (67). In order to fully describe articular involvement in CINCA/NOMID patients, Hill *et al.* performed a radiological assessment (including MRI) on 20 patients, confirming that the arthropathy was caused by abnormal endochondral bone formation leading to a heterogeneously calcified mass in the bone physis (66). Moreover, biopsy samples obtained from 2 patients

Table II. Overview of joint and muscle involvement in the four main monogenic autoinflammatory diseases.

Disease	Joint/Muscle involvement	Disease Manifestations
Familial Mediterranean fever	Joint involvement	- Active arthritis (during fever) – often involving the large joints of lower limbs in the form of non-erosive monoarthritis - Oligoarthritis and involvement of joints in the upper part of the body are also described - Subacute arthritis (lasting up to 2 weeks) – mainly affecting large lower limb joints in the form of mono- or oligoarthritis. Sometimes leading to flexion contractures - Chronic arthritis (recurrent articular flares or a unique prolonged episode) – generally affects knees and hips with destructive sequelae up to aseptic necrosis of the femoral head and joint replacement - Sacroiliitis – especially in patients with the M694V mutation. This mutation could represent a susceptibility factor for enthesitis-related arthritis
	Muscle involvement	- Spontaneous or exercise-induced myalgia - Protracted febrile myalgia syndrome –especially in patients with the M694V mutation; myalgia and severe asthenia are accompanied by fever and other FMF-related symptoms and transient vasculitic purpura - Myositis – an unusual manifestation of FMF - Colchicine-induced myotoxicity – proximal muscle weakness, increased CPK levels, unspecific changes at electromyography; vacuolar changes of muscle cells at biopsy
Cryopyrin-associated periodic syndromes	FCAS MWS CINCA/NOMID	Joint and muscle involvement
		- Arthralgia, myalgia - Arthritis, arthralgia, myalgia - Chronic arthritis characterised by conspicuous structural changes with bony overgrowth and joint deformities
Tumour necrosis factor receptor-associated periodic syndrome	Joint involvement	- Arthralgia is the most frequent manifestation - Arthritis generally affect large joints, but small joints may seldom be involved - Sacroiliitis is anecdotally reported in TRAPS
	Muscle involvement	- Myalgia is related to a monocytic fasciitis rather than myositis
Mevalonate kinase deficiency	Joint involvement	- Arthralgia in most cases - Arthritis of large joints with a non-erosive evolution is observed in one half of patients; flexion contractures, bone deformity, and erosions are observed in less than 10% of cases
	Muscle involvement	- Myalgia is observed in one half of patients

CINCA: chronic infantile neurologic cutaneous and articular syndrome; CPK: creatine phosphokinase; FCAS: familial cold autoinflammatory syndrome; FMF: familial Mediterranean fever; MWS: Muckle-Wells syndrome; NOMID: neonatal-onset multisystem inflammatory disease; TRAPS, tumour necrosis factor receptor-associated periodic syndrome.

showed poorly organised chondrocyte columns (66). In accordance with this last finding, the *NLRP3* gene has been found to be highly detectable in chondrocytes from patients with CINCA/NOMID, thus supporting a role of cryopyrin in cartilage remodelling through apoptosis (4).

Tumour necrosis factor receptor-associated periodic syndrome

Clinical manifestations of TRAPS usually start during childhood and adolescence, however, an adult presentation can occur in up to 20% of patients, especially in subjects carrying low-penetrance mutations (11, 16, 18, 20, 68). Fever attacks typically last from 1 to 3 weeks and are variously associated with periorbital oedema, myalgia, ar-

thralgia, conjunctivitis, and abdominal pain. However, many other inflammatory features may be encountered, including atypical manifestations (9, 13, 68-74). Among others, eye involvement can also occur in the form of conjunctivitis and uveitis (75-77), while skin lesions may include erysipelas-like erythema, oedematous plaques, and urticarial, reticular or serpiginous rash. Nevertheless, migrant macular erythematous rash in the form of monocytic panniculitis overlying an area of muscle pain is the most frequent skin manifestation in TRAPS (78, 79).

Although described in less than 10% of patients, monocytic fasciitis represents the most characteristic musculoskeletal TRAPS feature. It manifests with warm and tender skin patches accom-

panied by myalgia and muscle tenderness with a typical migratory pattern (73, 75, 80). Histologically, a monocytic infiltrate may be observed followed by extensive destruction of fascia, collagen, and perimysium, while muscle myofibers and endomysium are spared suggesting that muscle pain, which is a frequent finding especially in patients with high-penetrance mutations (16), is not related to an inflammatory involvement of the muscle (81).

In addition to muscle aches, TRAPS attacks are commonly accompanied by arthralgia, while arthritis is a less frequent finding that mainly affects large joints in a non-erosive manner (82). Nevertheless, Lopalco *et al.* recently described three TRAPS patients suffering from chronic arthritis in the small

joints of the feet and wrists (83). In addition, sacroiliitis has been anecdotally reported in TRAPS, suggesting a careful evaluation of low-back pain in such patients (74, 83, 84). Of note, Cantarini *et al.* reported on a patient carrying the low-penetrance mutation R92Q and presenting with sacroiliitis and pericarditis as the sole inflammatory manifestations (84).

Although TRAPS is typically characterised by recurrent inflammatory bouts, some manifestations may persist among acute attacks in a chronic fashion, especially in patients with delayed onset and low-penetrance mutations (16). In this context, Quillinan *et al.* evaluated 5 TRAPS patients with persistent myalgia, arthralgia, malaise, and fatigue between acute febrile attacks and identified either subclinical fasciitis or arthritis with whole-body MRI in 4 out of 5 cases (85).

Mevalonate kinase deficiency syndrome

The severity of MKD, also known hypergammaglobulinemia-D syndrome (HIDS), depends on the residual enzymatic function of the mutated protein. In general, two different inflammatory entities can be described in relation to the mevalonate kinase defect, with MKD being the milder type and mevalonic aciduria the more severe phenotype. Specifically, MKD is associated to an enzymatic activity ranging from 1 to 10% of normal levels, while mevalonic aciduria corresponds to an enzymatic activity of approximately 1% (86). MKD is clinically characterised by febrile attacks, cervical lymphadenopathy, maculopapular rash, mucosal ulcers, and severe abdominal pain often correlated with diarrhoea and/or vomiting (87). Inflammatory bouts last 4 to 7 days and recur every 4 to 6 weeks. Symptoms may be triggered by immunisations and onset occurs up to 5 years of age in almost all cases; however, 78% of cases experience the onset of symptoms within the first year of life (88, 89). In addition to symptoms encountered in MKD, mevalonic aciduria is also characterised by neurological impairment, severe growth retardation, and early death.

Polyarthralgia is recorded in approximately 80% of patients, while non-erosive arthritis of large joints is described in more than half the cases. An analysis of the largest currently available cohort of MKD patients from the Eurofever registry identified musculoskeletal involvement in 89 out of 113 patients, arthralgia in 80 cases, myalgia in 64 out of 112 subjects assessed, and arthritis in 31 out of 109 patients (89). Arthralgia, myalgia, and arthritis were also identified in 15%, 18%, and 9% of patients, respectively, during fever-free periods. A severe musculoskeletal involvement, defined as flexion contractures, bone deformity, bone erosions, persistent arthritis, osteitis, or osteolytic lesion, was identified in 8 out of 110 (7.3%) patients assessed (89).

Conclusions

Musculoskeletal involvement is a frequent finding in patients with monogenic AIDs, ranging from acute myalgia and arthralgia to severe arthritis, fasciitis, and chronic joint manifestations able to induce bone erosions and conspicuous deformities, as summarised in Table II. Therefore, physicians dealing with these disorders should be familiar with joint and muscle manifestations, some of which are very useful for diagnostic purposes, such as the monoarthritis of a large lower limb joint in FMF and the monocytic fasciitis in TRAPS. Indeed, their prompt recognition may reduce the diagnostic delay and allow an early appropriate therapeutic management.

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