Autoinflammatory diseases in childhood

Betul Sozeri¹*, Ozgur Kasapcopur²

¹Department of Pediatric Rheumatology, Medical Faculty, Ege University, Izmir, Turkey; ²Department of Pediatric Rheumatology, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey

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ABSTRACT

Autoinflammatory diseases are defined as recurrent attacks of systemic inflammation that are often unprovoked (or triggered by a minor event) related to a lack of adequate regulation of the innate immune system. Within the past decade, the list of autoinflammatory diseases has included cryopyrin-associated periodic syndromes, familial Mediterranean fever, mevalonate kinase deficiency, tumor necrosis factor receptor-associated periodic syndrome, hereditary pyogenic disorders, pediatric granulomatous autoinflammatory diseases, idiopathic febrile syndromes (systemic-onset juvenile idiopathic arthritis, PFAPA syndrome), complement dysregulation syndromes and Behçet’s disease. The hereditary autoinflammatory diseases are a group of Mendelian disorders characterized by seemingly unprovoked fever and localized inflammation. Autoinflammatory diseases can activate NOD-like receptors and inflammasome products including especially interleukin 1β. In this review, it focuses on how recent advances have impacted hereditary autoinflammatory diseases.

KEYWORDS

Autoinflammatory Diseases; Familial Mediterranean Fever; Diagnosis; Pathogenesis; Treatment

1. INTRODUCTION

The term autoinflammatory diseases (AID) describes a group of inherited disorders that are characterized by exaggerated innate immune responses leading to recurrent episodes of fever and inflammation that affects multiple organs including the skin, serosal membranes, joints, gastrointestinal tube, central nervous system, etc.

Most AIDs typically manifest in childhood, although a limited number of patients may experience disease onset during adulthood. The autoinflammatory diseases have included cryopyrin-associated periodic syndromes, familial Mediterranean fever, mevalonate kinase deficiency, tumor necrosis factor receptor-associated periodic syndrome, hereditary pyogenic disorders, pediatric granulomatous autoinflammatory diseases, idiopathic febrile syndromes (systemic-onset juvenile idiopathic arthritis, PFAPA syndrome), complement dysregulation syndromes and Behçet’s disease.

The aim of this review is to focus on how recent advances have impacted diagnosis, pathogenesis, and treatment of hereditary autoinflammatory diseases.

2. PATHOGENESIS

These conditions can be distinguished from autoimmune disorders by the absence of autoantibodies or antigen specific T cells. The disease mechanisms in AIDs involve innate immune regulation of cytokines and neutrophilic inflammation [1]. IL-1β is a potent pro-inflammatory cytokine, which is synthesized early in response to infection and tissue injury by cells of the innate immune system [2]. (Figure 1).

The cells of the innate immune system, primarily epithelial, dendritic, polymorphonuclear, and macrophage cells, act not only as an immediate barrier, but also as effectors in the evolution of the inflammatory response. The innate immune system recognizes pathogen-associated molecular patterns and damage associated molecular patterns by several complex mechanisms, involving cell associated pattern recognition receptors and soluble recognition molecules. Nucleotide oligomerization domain—like receptors (NLRs) within the cell and other
receptors further mediate intracellular innate immune system processes and development of the inflammatory response. NLRPs (NLRs with pyrin-domain-containing proteins) are a subfamily of the NLRs. NLRP3 assembles other proteins to form the inflammasome complex in response to cytoplasmic pathogen-associated molecular patterns and damage-associated molecular patterns, which also triggers the expression of proinflammatory genes by transcription factors (e.g., nuclear factor-kB). The inflammasome complex involving NLRP3 recruits and activates caspase 1, a protease that cleaves pro-interleukin (IL)-1β and IL-18 to their active forms. The common pathogenic pathway of the autoinflammatory syndromes involves the excessive production and activity of these proinflammatory cytokines and molecules, not as a result of external stimuli but as a result of mutations in different proteins that regulate these pathways [1,3].

2.1. Familial Mediterranean Fever (FMF)

Familial Mediterranean fever is an autosomal recessive disease characterized by recurring self-limited short episodes of fever and serositis, resulting in pain in the abdomen, chest, joints and muscles. It is the most common of the periodic hereditary fevers. This mainly affects Middle Eastern populations and other ethnic groups living around the Mediterranean basin, such as Jews, Armenians, Turks, Arabs, with high prevalence (1/200-1/1000); also, it is not considered rare in Italy, Spain and Greece [4-6]. Almost 60% of patients have a disease onset before 5 years and almost all patients before the second decade of life [6,7].

Clinical presentation:

The disease typically presents with recurrent episodes of fever, associated with acute abdominal pain and large joint arthritis that last 1 to 3 days [8]. Generally, a typical attack lasts between 12 and 72 hours, and raises a peak within 12 hours of onset. The interval between attacks is variable from few weeks to months or years. The attack may be triggered by common factors such as cold exposure, emotional or physical stress, infections or menstruation [9].

Recurrent fever is characterized by temperature from 38°C to 40°C, it can partially respond to antipyretics or steroids administration, while antibiotics do not have any effect. In course of fever, laboratory exams can typically show a neutrophilic leukocytosis, together with the increase of inflammation indexes, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum amyloid-A (SAA) and fibrinogen, which disappear in inter-current well-being periods, except in patients with persistent subclinical inflammation [10].

Abdominal pain: These are experienced by 90% of affected individuals and start with the sudden onset of fever and pain affecting the entire abdomen [1]. Physical examination reveals board-like rigidity of the abdominal muscles, rebound tenderness, abdominal distension, and loss of peristaltic sounds. Radiographs reveal multiple
small air-fluid levels in the small bowel. Joint involvement: Large joints may be affected by arthritis or arthralgia in more than 50% of patients (chiefly knees, hips and ankles). These occur suddenly, and may be precipitated by minor trauma or effort, such as prolonged walking. Gradual resolution of the signs and symptoms are after peaking in 24-48 hours. The attacks are commonly in the hip or knee but may occur in other joints such as the ankle, shoulder, temporomandibular joint, or sternoclavicular joint. The joint remains swollen and painful, as in chronic monoarthritis [11,12].

Chest attacks: Pleuritis is experienced by approximately 45% of patients with FMF and are the sudden onset of an acute, one-sided febrile pleuritis, which resolves within 48 hours. Pericarditis is a rare occurrence. It is characterized by retrosternal pain [13]. Other clinical manifestations of FMF include protracted febrile myalgia, which generally responds to steroid therapy [14], and also erysipelas-like erythema, aseptic meningitis (also known as Mollaret syndrome) and vasculitides (Henoch-Schönlein purpura and polyarteritis nodosa) entities that are generally present in ≤5% of patients [15].

Tel Hashomer criteria (Table 1) are often used to make the diagnosis [16]. Yalçinkaya and colleagues recently validated the sensitivity and specificity of Tel Hashomer criteria in 170 FMF children [17]. The results were compared with sensitivity and specificity of a proposed new set of 5 criteria for the FMF diagnosis in childhood, including fever (axillary temperature ≥38°C), abdominal pain, chest pain, arthritis (for all the conditions the number of the attacks has to be ≥3, with a 6-72 hours of duration), and family history of FMF. The presence of 2 of these 5 criteria resulted to have a higher specificity compared to that of Tel Hashomer criteria (93.6% versus 54.6%, respectively) (Table 2) [17]. The validation of the Yalçinkaya criteria in a French population of children using an appropriate control group did not show a better performer mutations clustered in exon 10) and E148Q (clustered in exon 2) are considered as common mutations related to FMF [24-26]. Mattit et al. [27] tested for these mutations in 83 unrelated patients who fulfilled the international FMF criteria and 242 unrelated apparently healthy controls. Among the 83 patients, 30.1% were homozygotes, 39.8% compound heterozygotes, 19.3% heterozygotes, and 10.8% had no identifiable mutation.

M694V is more commonly seen among Sephardic Jews, Turks, and Armenians; E148Q among European and Turks patients; M694I is more frequent among Arabs; M680I is detected particularly among Armenians [27-31].

The carrier rate for FMF has been calculated to be as high as 1.3 - 1.7 in North African Jews, Iraqi Jews, Armenians, and Turks [29-32].

Studies have cast considerable doubt on whether FMF is, in fact, a traditional autosomal recessive disease. Booty et al. [33] performed an extensive search for a second MEFV mutation in 46 patients diagnosed clinically as having FMF and carrying only one high-penetrance FMF mutation. They did not identify a second MEFV mutation in any of the patients screened, and haplotype analysis did not identify a common haplotype that might be associated with the transmission of a second FMF allele. They also found no significant difference in pyrin levels between patients with a single mutation and those with a double mutation. The authors concluded that there exists a significant subset of patients with FMF who have only one MEFV mutation and that in such patients detection of a single mutation seems to
be sufficient in the presence of clinical symptoms for the diagnosis of FMF and the initiation of a trial of colchicine.

In the literature, vary authors discussed possible explanations as to how a person carrying only one MEFV mutation can present with the clinical manifestations [33-35]: one of these explanation is the presence of less common mutations missed by routine testing, second one is digenic inheritance (the interaction of two genes resulting in the expression of a phenotype) is known to occur with autoinflammatory diseases. The third possibility is the epigenetics which changes in gene expression that do not involve changes in the underlying DNA sequence.

Complications:

The most important long-term complication is progressive systemic type AA amyloidosis [36,37]. AA amyloidosis is caused by the extra-cellular deposition of amyloid fibrils, which culminates in multi-organ dysfunction, particularly of the kidneys.

Treatment:

Colchicine which is a tricyclic alkaloid extracted from two plants of the lily family is the principal therapy in FMF [38,39]. Colchicine reduces attack frequency, decreases severity and shortens duration of the acute attacks in most FMF patients [38,39]. Colchicine inhibits microtubule polymerization by binding to tubulin, marked effects are exerted on leukocytes and, as recently demonstrated, on NACHT-LRRPYD- containing protein 3 (NALP3; cryopyrin) activity in macrophages [40,41]. Also, colchicine modulates the expression of pyrin and interacts in the cytosol. Its most effective results have been obtained in the prophylaxis of FMF, while the administration during the attacks is ineffective; during the attack a non-steroidal anti-inflammatory drug can be administered [42]. The dose of colchicine in adults is 1 mg/day. In children, dosage should be arranged according to age: The oral starting doses should be: ≤0.5 mg/day (for children <5 years of age); 1.0 mg/day (for children 5-10 years of age); above the age of 10 years, patients can take more than 1.0 mg colchicine daily [39,43]. Colchicine dosage should be increased in a stepwise fashion (e.g. 0.25 mg/step) up to a maximum of 2.0 mg/day in order to control the disease in patients who do not clinically respond to the standard dosage (therapy).

Colchicine often leads to gastrointestinal side effects. Padeh et al. [44] reported the most common side effect is diarrhea and appear the initiation of treatment. Also, colchicine can enhance B12 malabsorption and in rare cases can cause alopecia and bone marrow suppression. Macrolides, diltiazem, grapefruit and cyclosporine should not be taken with colchicine as fatal toxicity can occur [45].

Colchicine prevents febrile attacks in more than 60% of patients and significantly reduces the number of attacks in another 20% - 30%. Five to ten percent of patients do not respond to therapy, but most of them are non-compliant [4,39].

The patients who had either incomplete disease control on colchicine alone, or were unable to use colchicine due to side effects, or had FMF in association with vasculitis who can be treated with several agents: Corticosteroids, Interferon alpha, TNF blocking agents, IL-1 blocking agents (Anakinra-canakinumab) [39,46]

2.1.1. Mevalonate Kinase Deficiency

Periodic fever associated with mevalonate kinase deficiency (MKD) was originally identified in 1984 in six patients of Dutch ancestry with a long history of recurrent attacks of fever of unknown cause and a high serum Ig D level by Jos van der Meer in 1985 [47]. This is a metabolic disorder resulting from insufficient activity of the enzyme mevalonate kinase, coded by the MVK gene involved in cholesterol and isoprene biosynthesis. Mevalonate kinase activity is usually reduced to 5% - 10% of normal with excessive accumulation of mevalonic acid [48]. Increased mevalonic acid or isoprenoid end products cause IL-1 overproduction through the activation of the inflammasome [49,50].

The disease usually starts in infancy or early childhood: typical flares are irregular, last 3-7 days, have an abrupt onset and can be induced by vaccinations, infections and menses, being staggered by asymptomatic periods of several weeks [51]. Severe abdominal pain often accompanied by vomiting and/or diarrhea is the most frequent manifestation associated with fever attacks. Irritability and cervical lymphadenopathy are common features too and splenomegaly may be found in about half of patients during acute episodes. Marked lymph node enlargement and splenomegaly help to distinguish clinically MKD from FMF [52]. mucocutaneous manifestations are frequent and include erythematous macules. Neutrophilia and elevated acute phase reactants are present during fever attacks. Increased plasma levels of IgD (>100 UI/ml) during fever episodes and in basal conditions have been considered in the past as a hallmark of the disease. However, the specificity of this finding is low [53,54]. The polyclonal elevation of serum IgD is found mostly in patients older than 3 years, but this is not exclusive for MKD, while in 20% of patients there is no increase of serum IgD [10]. A clarifying clue to the diagnosis is the increased urinary excretion of mevalonic acid during febrile flares [54]. Amyloidosis is rare seen in MKD (only in 2.9% of cases) [55].

MKD is an autosomal recessive disease. So far more than 130 substitutions or deletions of the MVK gene have been reported [56] (http://fmf.igh.cnrs.fr/infevers/).
The most common mutation in MVK gene is the V377I variant, which is exclusively associated with the mild phenotype of MKD with some residual MVK activity [57]. Some variants (i.e., V310M, A334T) are closely associated with a severe MA phenotype and severely impaired cellular MVK activity [58].

Fever attacks usually respond dramatically to the administration of steroids (prednisone: 1 mg/kg/day in a single dose or with a short course of 3 to 5 days). Different reports have shown the potential benefit of anti-tumor necrosis factor therapy with etanercept (0.8 mg/kg/week by subcutaneous injection) and anti-IL-1 therapy with anakinra (subcutaneously administered at the daily dosage of 1 mg/kg/day) [59,60]. However, due to the high frequency of the fever episodes, some patients may need almost continuous treatment.

2.1.2. Tumor Necrosis Factor Receptor-Associated Periodic Fever Syndrome

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) exhibits autosomal dominant inheritance pattern and long-lasting fever episodes. TRAPS is caused by missense mutations in the p55 TNF receptor (or TNFR1A), encoded by the TNF super family receptor 1A gene [61] (TNFRSF1A). A total of 114 sequence variants of the TNFRSF1A have been recorded so far; of which 75 are associated with a TRAPS phenotype [56] (http://fmf.igh.cnrs.fr/infevers/). There are an increasing number of studies evaluating the role that specific TNFRSF1A mutations might have in the establishment of a constitutive inflammation through the secretion of proinflammatory cytokines as IL-1, interleukin-12 and interleukin-8 [62]. The status of two sequences, R92Q and P46L, has not been fully determined [63-67]. These mutations are frequently seen in normal controls (up to 9% of the population), do not alter the protein structure, and may represent milder mutations of low penetrance [3,67].

The age of onset can be variable (from infancy to over 50 years) and the clinical picture is characterized by febrile episodes lasting 3 - 4 weeks, even though attacks shorter than 5 days have been reported, recurring at least 2 - 6 times each year, combined with abdominal pain, diarrhea, arthralgia, localized myalgia and variable migratory skin manifestations [10,66]. Typical are centrifugal muscle edema with chronic fasciitis and the characteristic periorbital edema with painful conjunctivitis [68].

In the most severe forms of TRAPS, clinical signs of inflammation are almost permanent and require daily use of corticosteroids, leading to dependence and requiring the use of other anti-inflammatory drugs. Colchicine does not seem to prevent recurrences of TRAPS attacks. Etanercept and other TNF inhibitors have provided various degrees of clinical improvement and allowed savings of steroids in many cases [69-71]. The IL-1 receptor antagonist anakinra has also shown substantial clinical benefit in TRAPS patients and prevented disease relapses at the dose of 1.5 mg/kg/day by subcutaneous injection for a period of 15 days after the attack onset [72].

2.1.3. Cryopyrin-Associated Periodic Syndromes

Three autosomal-dominant syndromes constitute cryopyrin-associated periodic syndromes (CAPS): (1) familial cold autoinflammatory syndrome (FCAS), (2) Muckle-Wells syndrome (MWS), and (3) neonatal-onset multisystem inflammatory disease (NOMID). They are caused by single base mutations on the NLRP3 gene (NOD-like receptor 3, also known as cold-induced autoinflammatory syndrome 1, CIAS1) located on the long arm of chromosome 1 encoding the protein cryopyrin [73,74]. Mutations of the NLRP3 gene are found in almost 70% of patients with a CAPS phenotype. No NLRP3 mutations are found in about 50% of patients with NOMID and 25% to 33% of patients with MWS; these patients have a similar phenotype and response to treatment as mutation-positive patients [75]. Mutations lead to cryopyrins with gain-of-function, which cause a constitutive activation of the inflammasome and IL-1 overproduction [76]. FCAS and MWS are familiar, while cases of NOMID are sporadic.

FCAS is characterized by urticarial rash and fever spikes of short duration (usually <24 h) induced by cold exposure. Arthralgia and conjunctivitis are also common. Other symptoms observed following cold exposure include profuse sweating, drowsiness, headache, extreme thirst and nausea [77]. Muckle-Wells syndrome is characterized by recurrent episodes of urticarial and fever that may develop in early infancy. Acute phase reactants are elevated during fever episodes, and may also persist slightly increased during free intervals. During the course of the disease, neurosensory deafness (60%) and polyarthritis may develop [78]. Amyloid A (AA) amyloidosis is a complication of the late stage of the disease [79-81]. NOMID is the most severe expression of NLRP3 mutations: patients present a chronic rash at birth and develop a characteristic hypertrophic arthropathy involving both knees with premature ossification of patella, chronic aseptic meningitis and papilledema [82]. Many affected individuals present a dysmorphic faces characterized by frontal bossing, saddle back nose and midface hypoplasia, causing a sibling-like resemblance [68]. Mental retardation and seizures have also been reported. Patients exhibit persistent elevation of acute phase reactants, leukocytosis and chronic anemia [83-86]. Renal amyloidosis has been observed in 25% of MWS patients and 20% of NOMID ones [87].
some 100 variants have been associated with any of the 3 phenotypic forms (http://fmf.igh.cnrs.fr/infevers) [56].

Almost all the observed mutations are found in exon 3 of the NLRP3 gene, coding for the NACHT domain of cryopyrin that plays a crucial role in oligomerisation of the protein.

The pivotal role of cryopyrin in driving caspase-1 activation and the massive secretion of mature IL-1β observed in cryopyrin-mutated individuals suggested that anti-IL-1 treatment could represent an effective therapy. Anakinra has been the first biologic designed for the selective blockade of IL-1: however, its short plasma half-life requires a daily subcutaneous administration at the dose of 1 - 3 mg/kg/day by subcutaneous injection (only some patients with MWS might tolerate anakinra administrations at least every 2 days, remaining in ongoing remission); the dosage required for NOMID is variable and might need escalations varying from 1 to 10 mg/kg/day [88]. Two more recent IL-1 antagonists have been licensed for FCAS and MWS, rilonacept (a dimeric fusion protein, designed for subcutaneous administration at weekly intervals, FDA-approved in 2008) and canakinumab (a fully human monoclonal anti-IL-1 antibody, designed for subcutaneous administration once every 4 - 8 weeks, FDA-approved in 2009), both with a highly favorable safety profile [89,90].

The most frequent features of autoinflammatory diseases are compared in Table 3. Diagnostic algorithm was shown in Figure 2.

2.2. NLRP12-Associated Autoinflammatory Disorder

This disorder also known as familial cold autoinflammatory syndrome 2 (FCAS 2) which is a rare genetic disease caused by NLRP12 mutations transmitted with autosomal dominant inheritance. NLRP12 has been shown to play a role in the regulation of the pro-inflammatory NF-κβ pathway, accelerated secretion of IL-1 secondary to a deregulated redox state has been suggested as an alternative pathogenic mechanism [91,92]. These patients suffer from recurrent bouts of fever lasting 5 - 10 days accompanied by headache, joint symptoms and skin rash triggered by cold exposure.

2.2.1. Deficiency of the Interleukin-1-Receptor Antagonist (DIRA)

DIRA is a autosomal recessive autoinflammatory syndrome, due to the deficiency of the interleukin-1-receptor antagonist (IL1RN). The patients so far described exhibit homozygous truncating mutations in the IL1RN gene.

The cause is a missense-nonsense mutation (or a 175-db deletion) in the IL1RN gene at the long arm of chromosome 2 that encodes the IL-1 receptor antagonist, leading to unopposed IL-1 stimulation [93].

It begins around birth with multifocal osteomyelitis, periostitis, and pustulosis. Persistent elevation of acute phase reactants (ESR and CRP) is observed from birth [52]. The skin manifestations range from groupings of small pustules to a generalized pustulosis. The bone manifestations include osteolytic lesions with a sclerotic rim, epiphyseal ballooning of multiple distal and proximal long bones, widening of ribs and clavicles, heterotopic ossification or peristomal cloaking of the proximal femoral metaphysis and periostal elevation of the diaphysis [93].

2.2.2. Pyogenic Sterile Arthritis, Pyoderma Gangrenosum, and Acne Syndrome (PAPA)

This autosomal dominant disease is caused by mutations in proline serine threonine phosphatase-interacting protein [PSTPIP1, or CD2-binding protein 1 (CD2BP1)], also interacting with pyrin [94,95]. The arthritis usually has its onset in early childhood. It is pauciarticular in nature, and is characterized by recurring inflammatory episodes that resemble septic arthritis and lead to accumulation of pyogenic, neutrophil-rich material within the affected joints, which ultimately results in significant synovial and cartilage destruction [96,97]. Dermatological manifestations are onset usually during the second decade of life, and are characterized by debilitating, aggressive, ulcerative skin lesions. Cultures of the skin lesions and joint fluid of these patients are sterile. PAPA syndrome treated with oral glucocorticoids or anti TNF/IL-1 therapy [66].

2.2.3. Early-Onset Sarcoidosis (EOS) (Sporadic Granulomatous Arthritis) and Blau’s Syndrome (Familial Granulomatous Arthritis)

Blau syndrome is a rare autosomal dominant disorder characterized by granulomatous polyarthritis, panuveitis, cranial neuropathies, and exanthema [98,99]. The gene responsible for Blau syndrome, NOD2/CARD15,
Table 3. Summary of the general clinical signs of other autoinflammatory diseases in childhood.

<table>
<thead>
<tr>
<th></th>
<th>Mevalonate kinase deficiency</th>
<th>Tumor necrosis factor receptor-associated periodic fever syndrome</th>
<th>Familial cold autoinflammatory syndrome</th>
<th>Muckle–Wells syndrome</th>
<th>CINCA syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset age</td>
<td>First year of life (median age of 6 months)</td>
<td>Median age of 3 years</td>
<td>First infancy</td>
<td>Infancy, adolescence</td>
<td>Neonatal (even prenatal) period</td>
</tr>
<tr>
<td>Duration of clinical signs</td>
<td>3 - 7 days</td>
<td>7 days or even 3 - 4 weeks</td>
<td>&lt;24 h</td>
<td>Different days or Sub-continuous</td>
<td>Continuous with variable exacerbations</td>
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<tr>
<td>Eye involvement</td>
<td>Uveitis, retinal dystrophy (unusual)</td>
<td>Periorbital edema and conjunctivitis</td>
<td>Conjunctivitis</td>
<td>Conjunctivitis</td>
<td>Chronic papilledema, optic nerve atrophy, visual loss</td>
</tr>
<tr>
<td>Skin manifestations</td>
<td>Maculo-papular, urticarial, nodular, nummular or vasculitic</td>
<td>Erythematous serpiginous migratory rash, celluliitis-like plaques</td>
<td>Cold-induced urticaria-like rash</td>
<td>Evanescent urticaria-like rash</td>
<td>Persistent polymorphous urticaria-like rash</td>
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<tr>
<td>Musculo-skeletal symptoms</td>
<td>Arthralgia, non-erosive arthritis, Nonspecific myalgia</td>
<td>Arthralgia, tenosynovitis</td>
<td>Arthralgia or joint stiffness</td>
<td>Lifelong arthralgias, non-erosive polyarthritides</td>
<td>Deforming osteo-arthropathy of large joints, abnormal premature patellar ossification, digital clubbing</td>
</tr>
<tr>
<td>Systemic signs</td>
<td>Splenomegaly, Lymph node Enlargement, Serosal involvement, Lymph node enlargement</td>
<td>Fever spikes of short duration and profuse sweating (after cold exposure), thirst</td>
<td>Fever, drowsiness</td>
<td>Recurrent fever with shivers, chronic aseptic meningitis</td>
<td></td>
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<tr>
<td>Specific features</td>
<td>Oral aphthosis</td>
<td>Localized myositis and fasciitis</td>
<td></td>
<td>Dysmorphic Features (Frontal bossing, saddle nose, midface hypoplasia)</td>
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