Review

Autoinflammatory diseases: an update of clinical and genetic aspects

Q. Yao and D. E. Furst

To review clinical manifestations and genetic features of the autoinflammatory diseases, a group of rare, genetically defined diseases which have been newly grouped into a coherent whole. We performed a literature review using the keywords ‘periodic fever syndrome’, ‘autoinflammatory disease’ and ‘therapy’. All relevant original and review articles in English were reviewed. A case report of each autoinflammatory disease was excerpted from the literature and presented. This review summarizes the clinical manifestations, genetic analysis and therapy of FMF, TNF-α receptor-associated periodic fever syndrome, hyperimmunoglobulinaemia D periodic fever syndrome and cryopyrin-associated periodic fever syndrome. These diseases have periodic fever, are hereditary and recurrent, with elevated acute-phase reactants. Differentiating features of these disorders are tabulated. Autoinflammatory diseases have some commonalities in their presentation although they represent a relatively diverse group of genetically associated diseases.

Key words: Autoinflammatory disease, Familial Mediterranean fever, Tumour necrosis factor a receptor associated periodic fever syndrome, Hyperimmunoglobulinemia D periodic fever syndrome, Cryopyrin, Genetic analysis, Amyloidosis, Therapy, TNFα blocker, Interleukin-1 receptor antagonist.

Introduction

Autoinflammatory diseases (AIDs), also called periodic fever syndrome, refer to a group of rare hereditary recurrent unprovoked inflammation without high titres of autoantibodies or antigen-specific T lymphocyte in the absence of infection [1]. These diseases primarily include FMF, TNF receptor-associated periodic fever syndrome (TRAPS), hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS), and the cryopyrin-associated periodic syndrome (CAPS) including familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS) and neonatal onset multi-system inflammatory disease (NOMID)/chronic infantile neurological cutaneous and articular syndrome (CINCA).

A case of each AID will be presented and followed by a review focusing on the clinical manifestations, genetic analysis, pathogenesis, complication and therapy of these diseases.

Methods

A PubMed database search of the English language literature between 1975 and September 2007 was performed using keywords including periodic fever syndrome, AID, TRAPS, HIDS, MWS, FCAS and amyloidosis and therapy. All relevant original and review articles in English were reviewed for each of the diseases. A case report of each AID was excerpted from literature, reorganized and presented.

Results

FMF

Case report #1. A 35-yr-old Jewish male presented with recurrent episodes of arthralgia of the ankles since childhood, and he has had shoulder, knee, and foot pain for the last 10 yrs. Each episode lasted several weeks and was typically limited to a single joint. The patient also had episodic testicular pain and swelling, and a surgery was performed for a presumed hydrocele (no pathology report) without significant relief. Afterwards, he started experiencing recurrent episodes of oral ulcers and self-limiting severe abdominal pain, lasting 24-48 h. The abdominal pain was always followed by non-bloody diarrhoea. Fever was noted along with most episodes. The patient had no history of pleuritis, genital ulcers, rash or thrombotic events. His family history was unremarkable. His medications included a topical steroid for oral ulcers and various NSAIDs.

Physical examination confirmed oral ulcers, planter tenderness and mildly swollen knees and was otherwise unremarkable. Pathergy test was negative. Laboratory evaluation demonstrated elevated CRP of 3.0 mg/dl (normal 0-0.8) and negative RF. Urinalysis showed trace proteinuria. HLA B27 and B51 were negative. A single V726A mutation in the MEFV (Mediterranean fever) gene was identified. Imaging studies of joints were unrevealing.

This patient was on colchicine 0.6 mg p.o. three times a day with significant improvement of the oral ulcerations but severe diarrhoea led to discontinuation of the treatment. Pentoxifylline 400 mg 3 times a day was prescribed with improvement in oral ulcers. In spite of such treatment, articular, abdominal and testicular attacks remained present. The patient was then started on etanercept 25 mg subcutaneously twice a week, resulting in immediate reduction of the frequency, duration and severity of the joint attacks. No more abdominal or testicular attacks were recorded during 3 yrs of follow-up [2].

This case is typical for FMF in that it had recurrent attacks of fever and abdominal pain of <3 days’ duration, arthritis in lower extremities, elevated acute-phase reactant, positive MEFV gene and good response to colchicine therapy. The atypical clinical finding is testicular pain and swelling.

FMF is an autosomal recessive disease characterized by recurrent fever, serositis, arthritis and erysipelas-like erythema. Janeway and Mosenthal first reported the disease in 1908 [3].

Clinical manifestation. This disorder has been reported to occur primarily in Jews, Armenians, Turks and Arabs in the Mediterranean basin, central Asia and Japan [3]. It is the most prevalent form of AIDs [1]. It affects all ages, from infants to the elderly; however, 80% of the cases occur before the age of 20, in childhood or adolescence. The ratio of men to women is 1.5–2.0 : 1.0 [3].

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During episodic attacks, patients with FMF present with moderate-to-high fever which typically subsides spontaneously within 1–3 days [4, 5]. The fever is accompanied by painful serositis involving the peritoneum, pleura and/or even pericardium [6]. Patients are asymptomatic between the attacks although subclinical inflammation remains present [7].

Arthritis occurs, in decreasing frequency, in the knees, ankles and hips. Thirty-one percent of patients with FMF have arthritis with mono-articular, oligo-articular and polyarticular involvement (70, 26 and 4%, respectively) [8]. The arthritis of FMF is usually acute, episodic and self-limited with no sequelae [9]. Rarely, destructive arthritis may occur in the hips and knees, leading to joint replacement [10]. Synovial fluid analysis has shown different degrees of change from non-inflammatory to even septic-like pictures. Histologically, the synovitis is non-specific, affecting predominantly the synovial vasculature, although it may rarely be destructive in the articular cartilage [9, 11]. Sacroiliitis has been reported as well [12]. Erysipelas-like erythema usually occurs below the knees on the anterior leg or on the dorsum of the foot.

Laboratory findings [13] include leucocytosis and elevated acute-phase reactant proteins such as ESR, CRP, fibrinogen and serum amyloid A (SAA) protein.

Genetic analysis and pathogenesis. The MEFV gene was independently cloned by American [14] and French groups [15] in 1997. The protein encoded by the MEFV gene has been named pyrin by an American group for its role in anti-pyrexia; it is called Marenosrin by the French group for the Latin word Marenolstrum standing for Mediterranean Sea. To date there have been over 100 variants [16] in the MEFV gene identified, with the most commonly reported mutations being M694V, M6801 and V726A [17]. The MEFV gene and resulting pyrin protein are expressed in myeloid cells [18] including neutrophils, monocytes and eosinophils. It has been hypothesized [19] that the wild-type pyrin normally regulates inflammation via apoptotic speck-like protein. In FMF, however, the pyrin derived from the mutated gene seems to lose the ability to regulate the normal inflammatory process, particularly that part of the process due to the production of IL-1β and nuclear factor-kB (NF-kB). For genetic testing of the MEFV gene in FMF, DNAs are isolated from circulating lymphocytes and PCR, denaturing gel gradient electrophoresis and restriction enzyme analysis are used [20, 21].

Therapy. FMF generally responds to colchicine therapy. The therapeutic dose is usually 1–2 mg p.o. daily [22] and prophylactic use of colchicine may prevent amyloidosis [22, 23]. Approximately 5–10% patients with FMF do not respond to colchicine therapy [24]. Glucocorticoid use is not effective [25]. In colchicine-resistant patients, interferon-α has been reported to have modest disease-modifying efficacy [26]. Thalidomide, perhaps because it has some TNF-inhibiting features, has been reported to be beneficial as well [27]. TNF-α blockade with etanercept or infliximab has been reported to be effective for articular symptoms in particular and even for the amyloidosis of FMF [2]. Addition of anakinra has been efficacious in colchicine-resistant patients in two separate anecdotal case reports [28, 29].

TRAPS

Case report #2. A 27-yr-old woman presented in May 1999 with nephritic syndrome. She had had recurrent attacks of fever and abdominal pain since 18 months of age, requiring intermittent oral prednisolone. C353YTNRFSF1A mutation was identified and TRAPS was diagnosed. In the 6 months prior to the presentation, she had reported an increase in the frequency and severity of attacks. Twenty-four hour urinary protein excretion was 10.3 g, serum albumin 24 g/l (normal range 30–48 g/l) and serum immunoglobulin G (IgG) 2.7 g/l (normal range 6–15 g/l). Serum amyloid P (SAP) scan suggested amyloid in the kidneys and spleen.

Her father had TRAPS characterized by febrile abdominal attacks in his childhood and subsequent purpuric rash, chest pain and myalgia, and he later developed renal AA amyloidosis with resultant renal failure.

In October 1999, she commenced twice-weekly subcutaneous injection of 25 mg of etanercept. After 4 months of treatment, clinical improvement of the nephritic syndrome was apparent with 24-h urinary protein falling to 2.1 g, serum albumin rising to 30 g/l and IgG 5 g/l. Repeat SAP scan suggested regression of amyloidosis and glomerular filtration rate rose from 43 to 59 ml/min/1.73 m². Improvement of the nephritic syndrome was maintained by etanercept therapy for 2 yrs and accompanied by a dramatic reduction in inflammatory symptoms. Significant reductions in CRP and ESR occurred and SAA levels fell to <10 mg/l. Detectable plasma TNF-α levels rose on etanercept therapy.

This case is typical for TRAPS in that the patient had recurrent attacks of fever and abdominal pain in childhood, AA amyloidosis, positive family history, elevated acute-phase reactant, TNRFSF1A mutation and good response to etanercept therapy. The atypical clinical finding is a lack of arthralgia, rash and myalgia in Case #2 [30].

TRAPS is an autosomal dominant AID. An early report of 13 cases of the disease spanning three generations of an Irish family was named Hibernian (Irish) fever and published by Williamson et al. [31].

Clinical manifestations. This disease is characterized by recurrent fever at irregular intervals of weeks and months, accompanied by attacks of abdominal pain, pleurisy, localized myalgia involving a group of muscles and overlying erythematous macules and patches, mostly in the limbs [32]. The cellulitis-like subcutaneous inflammation moving distally on the upper limbs and orbital oedema are thought to be the most characteristic [32, 33]. Arthralgia occurs in 2/3 patients, involving peripheral joints in a monoarticular or oligoarticular fashion. Arthritis is less common [34]. One case of monocytic fasciitis has been reported [35]. TRAPS may be confused with juvenile idiopathic arthritis [36] and it may be coexistent with multiple sclerosis [37]. The disease attacks begin in childhood and can persist for up to 30 yrs. A single case of small-vessel vasculitis and panniculitis has been reported [38].

Laboratory findings [32] include leucocytosis, increased acute-phase reactant proteins and polycyonal elevation of Ig (IgA, in particular). Positive ANA and circulating immune complexes can, rarely, be detected.

Genetic analysis and pathogenesis. Mutations of the TNF receptor 1 (TNFR1) gene, TNFR superfamily 1A (TNFRSF1A), have been associated with the disease [39]. R92Q substitution is the most frequent TRAPS-related mutation [40]. Plasma TNFRSF1A protein level is low and the mutant form of TNFR1 on the cell surface is frequent. A plausible explanation for TNF-α-mediated inflammation in TRAPS is that, in the normal (non-mutated) state, the TNFR1 is released from the cell surface after interaction with TNF-α and it neutralizes TNF-α activity. However, in TRAPS associated with the mutated TNFRSF1A gene, the TNFR1 on the cell surface does not neutralize TNF-α, perhaps due to mutant TNFR1 protein misfolding and endoplasmic reticulum retention [41], so TNF-α-driven inflammation continues [42]. In addition, neutrophils of patients have been shown to be resistant to TNF-α-induced apoptosis [43]. These mechanisms may not explain all the clinical findings of the disease. DNAs are isolated from peripheral
blood mononuclear cells and are used for the analysis of TNFRSF1A [44].

Therapy. In TRAPS, glucocorticoids are usually efficacious [45]. Colchicine is ineffective in relieving or preventing the disease attacks [45]. Based on the mutation of TNFRSF1A in TRAPS, etanercept has been tried but with mixed results [46]. For example, Drew et al. [47] reported seven cases of TRAPS treated with etanercept 25 mg subcutaneously twice weekly over 42 weeks. Five cases demonstrated decreased acute-phase reactants and required less glucocorticoids, indicating that etanercept does not abolish inflammatory attacks but improves disease activity. In another report, positive therapeutic responses to etanercept treatment have been reported in two cases of systemic amyloidosis including the treatment of nephrotic syndrome and for small vasculitis and panniculitis [38]. In contrast, Jacobelli et al. [48] reported a failure of etanercept in treating two cases of TRAPS. Infliximab has also been tried in five patients but without efficacy [48]. Overall, the current consensus is that etanercept appears useful as a steroid-sparing agent, but response is partial or even absent in some cases.

HIDS

Case report #3. A German Caucasian man presented with nephrotic syndrome at the age of 22 and was found to have AA amyloidosis on renal biopsy. His renal function gradually declined, and dialysis was initiated within 3 yrs. He also reported a history of periodic febrile attacks from infancy, occurring every 6–8 weeks, more marked in winter. Accompanying symptoms characteristically included headache, cervical/inguinal lymphadenopathy and vomiting/diarrhoea. He was found to have IgG2/4 subclass deficiencies at the age of 9 yrs, and his attacks had been thought to represent recurrent infections, although he had received intravenous Ig supplementation without benefit. His serum IgD concentration was elevated at 104 mg/l (no normal value provided). DNA sequencing demonstrated mevalonate kinase (MVK) V377I and a previously unreported mutation MVK [44].

This case is typical for HIDS in that he had recurrent febrile attacks, lymphadenopathy, gastrointestinal symptom, elevated IgD and positive MVK gene. The atypical part is absence of arthralgia/arthritis and rash in Case #3. The deficiency of IgG subclass is an atypical laboratory finding also.

HIDS is an autosomal recessive inflammatory disease. An initial case report of six patients was documented by Van der Meer et al. [49] in The Netherlands in 1984.

Clinical manifestations. Recurrent high fever occurs every 4–6 weeks and lasts 3–7 days. The attacks of fever are accompanied by generalized lymphadenopathy and abdominal symptoms such as pain, vomiting and diarrhoea. HIDS' cutaneous presentation includes erythematous macules and papules, urticaria and other types of rash [50].

Symmetrical polyarthritis/arthralgia is present in 66% patients, primarily involving large joints such as the knees and ankles but without joint destruction [50]. Tendonitis has been reported as well [51]. Other symptoms and signs include headache, oral and genital ulcers. Caucasian patients account for the majority of the patients, with 60% being Dutch and French [52]. The median age at onset is 6 months old.

Laboratory findings include leucocytosis and raised acute-phase reactant proteins. Polyclonal IgD is elevated > 100 U/ml [49].

Genetic analysis and pathogenesis. The disease-defining gene, the MVK gene, was mapped to the long arm of chromosome 12 in 1999 [53]. The protein encoded by the MVK gene is MVK, a key enzyme in the biosynthesis of cholesterol and isoprenoid [54]. The mutated MVK gene causes MVK deficiency, resulting in an increase in urinary mevalonic acid excretion. It has been assumed that the increased mevalonic acid and lack of isoprenoid contribute to the inflammatory disease although direct evidence is lacking. Defective apoptosis of lymphocytes may play a role in HIDS [55]. The elevation of serum IgD is not specific to HIDS and its implication in the disease remains unclear [56]. However, IgD can cause significant increase in TNF-α and IL-1 levels, presumably contributing to the pathogenesis of HIDS [57]. DNASs are isolated from fibroblasts and lymphocytes/lymphoblasts for the analysis of the MVK gene in HIDS [58].

Therapy. No effective therapy is available for HIDS. Simvastatin, as an inhibitor of hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), reduces the duration of the attacks, perhaps because HIDS is a metabolic disease relating to MVK deficiency (involved in cholesterol synthesis) [59]. Trials of etanercept have produced mixed results [60]. Etanercept reduced the symptoms in two patients but there was no alteration of serum IgD or urine mevalonate. Anakinra, as an IL-1 antagonist (IL-1ra), was recently reported to be more effective than etanercept [61]. It aborted inflammation in a human vaccination model in which inflammatory attacks of HIDS are provoked [61]. NSAIDs, colchicine and glucocorticoids have been ineffective [62].

CAPS

Case report #4. A 22-yr-old white woman was hospitalized for the treatment of MWS. Her medical history began with hospitalization at age 8, when her right great toe arthritis developed, along with a transient urticarial rash. Laboratory work showed CRP of 60 mg/l (normal < 3) and a white blood cell count of 19,000/mm³. Treatment with NSAIDs for 4 days was effective. Approximately 1 yr after the first articlar symptom, the patient reported progressive high frequency hearing loss. Repeated audiographic examinations confirmed the presence of bilateral sensorineural deafness at age 12. At age 19, the patient required hearing aids. Flares of urticarial rashes, conjunctivitis, arthralgia and occasional synovitis occurred every 3–4 yrs.

Despite treatment with NSAIDs, the deafness and inflammatory symptoms were still present. The elevated CRP level and leucocytosis remained persistent. The patient did not receive any steroids or immunosuppressive treatment. A genetic study revealed a heterozygous E311K mutation in the cold-induced autoinflammatory syndrome 1 (CIAS1)/NALP3/PYPAF1 gene. The diagnoses of CAPS and, especially, MWS were therefore retained based on the bouts of arthralgia and arthritis, deafness and the absence of other neurological symptoms, meningitis or cold-induced urticaria. Because inflammatory symptoms and deafness were still present, treatment with anakinra (100 mg once daily by subcutaneous injection) was tried with good response. The CRP level was reduced by half after 1 month of treatment and nearly normalized after 2 months. Leucocytosis also normalized. At the third month, the patient did not require her hearing aids anymore. A repeat audiogram after 3 months of anakinra therapy demonstrated a nearly complete regression of deafness. No bouts of rash, fever or arthralgia were observed anymore. Although the patient tolerated the therapy well, a reduction in the dosage of anakinra was attempted from 100 mg daily to 100 mg every other day. Because the CRP started to raise, treatment with the initial dosage (100 mg daily) was therefore resumed, resulting in complete resolution of the inflammatory symptoms. After 18 months of treatment, the patient’s CRP level remained normal, and no recurrence of deafness was observed [63].

This case is typical for MWS in that the patient had urticarial rash, sensorineural deafness, arthritis, conjunctivitis, elevated
may contribute to the inflammatory process via its effects on IL-1, such as pyrin in FMF, the cryopyrin encoded by CIAS1 gene activation of caspase 1 and processing of IL-1 and IL-18 [68]. As a complex named the inflammasome [67] and it is essential for known as PYPAF1 or NALP3) [66] is part of a multiprotein associated mutations have been reported and most of them proteins and a high level of IL-6.

Chronic meningitis, uveitis and deforming arthritis as well as fever, NOMID is the most severe form of the disease characterized by Sensorineural hearing loss is a common finding of MWS. CINCA/junctivitis is a frequent presentation of FCAS after cold exposure. arthritis/arthralgia. FCAS is the mildest of CAPS [65]. Con-

Therapy. Based upon the aforementioned mechanisms in the disease process, therapy targeting IL-1β pathway has been used. Numerous case reports have recently showed that IL-1ra (anakinra), seems effective for CAPS variants including FCAS [71], MWS [72] and CINCA/NOMID [73]. For example, an 8-yr-old girl with FCAS recovered from her hearing loss and her CRP level normalized after starting IL-1ra [63]. In a multicentre clinical trial of IL-1ra in CINCA/NOMID [73], a total of 18 patients with CINCA/NOMID were treated with subcutaneous 1–2 mg/kg IL-1ra per day over 3 months. All 18 cases responded well, including disappearance of rash improving diary scores and improving acute-phase reactants.

Amyloidosis. Amyloidosis is caused by numerous diseases characterized by chronic inflammation; it is characterized by extracellular deposition of fibrils of aggregated proteins [75]. The amyloidosis in AID is known as reactive (type AA) amyloidosis and is the most common and serious complication of AID [76]. The reported prevalence of amyloidosis in FMF varies [77]. Renal amyloidosis is the most common form of amyloidosis. Using meta-analysis of 2482 cases of FMF collected from 35 medical centres in 12 countries, Touitou et al. [78] have recently reported that 11.4% had renal amyloidosis.

There were several case reports of amyloidosis in TRAPS [79] and four cases in HIDS [80]. Amyloidosis has also been reported with MWS [81]. Multiorgan involvement in amyloidosis including heart, liver and muscle may be present although renal amyloidosis is the most frequent manifestation [82]. The clinical presentations depend on the type of organ involved. SAA is an acute-phase reactant implicated in reactive amyloidosis. Under normal conditions, SAA is completely cleaved and degraded by cathepsin in macrophages; however, this process is impaired in patients with amyloidosis, resulting in intermediate AA protein polymerization and fibril formation. Severe AA amyloidosis carries a poor prognosis; however, effective control of the underlying inflammatory process will reduce the severity of amyloidosis and thus prolong survival [76]. In AID, amyloidosis is one of the most feared complications, but anecdotal data indicates that even for this complication, IL-1ra may be effective therapy.

Conclusions
Although the AIDs share some clinical features, such as (i) periodic fever of variable duration, (ii) hereditary and recurrent and (iii) elevated acute-phase proteins, there are differences that may be used to differentiate one from another (Table 2).

Treatment, too, has both similarities and differences, so that colchicine is the treatment of first choice for FMF; glucocorticoids seem best suited for TRAPS, TNF-α blockade and IL-1ra may work for HIDS and IL-1ra seems effective for CAPS.

### Table 1. Clinical features of CAPS

<table>
<thead>
<tr>
<th>Variant</th>
<th>Disease onset</th>
<th>Severity</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCAS</td>
<td>First 6 months of life</td>
<td>Mildest</td>
<td>Cold-induced fever, rash, arthralgia, conjunctivitis, headache</td>
</tr>
<tr>
<td>MWS</td>
<td>Childhood</td>
<td>Intermediate</td>
<td>Urticaria like rash, progressive hearing loss, fever, arthralgia</td>
</tr>
<tr>
<td>CINCA/NOMID</td>
<td>Neonat or early in infancy</td>
<td>Most severe</td>
<td>Non-pruritic urticaria like rash, CNS involvement including chronic aseptic meningitis, progressive sensorineural hearing loss and ocular change, disabling arthropathy</td>
</tr>
</tbody>
</table>

### Table 2. The major differentiating features

<table>
<thead>
<tr>
<th>Age at onset</th>
<th>FMF</th>
<th>TRAPS</th>
<th>HIDS</th>
<th>FCAS/NOMID/CINCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 yr</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>1–3 days</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>&gt;7 days</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Child (median 6 months old)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Infancy-1st 6 months</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>1–2 days</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fever</td>
<td>&lt;20 yr</td>
<td>&gt;20 yr</td>
<td>&gt;20 yr</td>
<td>&gt;20 yr</td>
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<tr>
<td>Serositis</td>
<td>++</td>
<td>++</td>
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<td>++</td>
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<tr>
<td>Musculoskeletal</td>
<td>Monarthritis</td>
<td>Monarthritis, localized Myalgia</td>
<td>Monarthritis, localized Myalgia</td>
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<tr>
<td>Cutaneous</td>
<td>Erysipeloid</td>
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<td>Adenopathy</td>
<td>Rare</td>
<td>Rare</td>
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<tr>
<td>Hearing loss</td>
<td>No</td>
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<tr>
<td>Amyloidosis</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Mode of inheritance</td>
<td>Recessive</td>
<td>Dominant</td>
<td>Recessive</td>
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<tr>
<td>Mutated gene</td>
<td>MEFV</td>
<td>TNFRSF1A</td>
<td>TNFR1A</td>
<td>TNFR1A</td>
</tr>
<tr>
<td>Gene product</td>
<td>Pyrin/marenoestrin</td>
<td>TNFR1A</td>
<td>TNFR1A</td>
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<tr>
<td>Therapy</td>
<td>Colchicine</td>
<td>Glucocorticoids</td>
<td>TNF-α blocker</td>
<td>IL-1-antagonist</td>
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*1–2 mg p.o. daily; *2Etanercept 25 mg s.c. twice weekly; *3Anakinra 1–2 mg/kg/day, s.c.
Rheumatology key message

- To better serve physicians who wish to know the new group of AIDs, we have presented a concise list of each disease and reviewed the literature systematically. We have been unable to find a review using similar approaches. In this way, our review may attract and better suit a wide range of readers.

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