JDDG
Journal of the German Society of Dermat
Check for updates

CME Article

Submitted: 9.8.2020
Accepted: 7.1.2021
Conflict of interest
None.

DOI: 10.1111/ddg.14332

Autoinflammatory syndromes

Barbara Meier-Schiesser[1], Lars E. French[2]

(1) Department of Dermatology, University Hospital Zurich, Zurich, Switzerland
(2) Department of Dermatology, Ludwig-Maximilians University Hospital, Munich, Germany

Section Editor
Prof. Dr. D. Nashan, Dortmund

Summary

Autoinflammatory syndromes are a steadily growing group of inflammatory diseases caused by abnormal regulations of the innate immune system. The clinical presentation is multifaceted, but recurrent fever, skin involvement, joint inflammation and other systemic symptoms of inflammation are characteristic. In contrast to classic autoimmune diseases, autoantibodies or specific T cells are not involved in the pathogenesis. In fact, innate immunity plays the most important role in autoinflammation. While activation of the innate immune system is usually self-limiting in healthy individuals, mutations and dysregulation can lead to chronic and excessive activation of innate immune responses and to the development of autoinflammatory diseases.

Introduction and concept of autoinflammation

The innate immune system plays a central role in the development of autoinflammatory syndromes.

The term "autoinflammatory syndromes" describes a group of inflammatory diseases that are triggered by an abnormal regulation of the innate immune system and become manifest in a variety of symptoms of systemic inflammation. Remarkably, the inflammation is always sterile and therefore no pathogens are involved. Likewise, no autoantibodies or specific T cells are detectable, which distinguishes this group of diseases from autoimmune diseases. A central role in autoinflammatory diseases plays the innate immune system. Important players of this system are cytosolic multiprotein complexes, so-called inflammasomes. The inflammasomes are essential components of the innate immune system, which represents the first line of defense against pathogens (pathogen-associated molecular patterns [PAMPs]) and the detection of danger signals (danger-associated molecular patterns [DAMPs]) in our body. PAMPs and DAMPs are recognized by specialized receptors (pattern recognition receptors, PRR). These include the toll-like receptors, NOD-like receptors (NLRs), C-lectin receptors and retinoic-acid-inducible-gene-1-like receptors. When PAMPs and DAMPs bind to NLRs, a complex cytosolic protein complex is formed – the inflammasome. Activation of the inflammasome leads to the cleavage of pro-interleukin (IL)-1β and the secretion of active IL-1β. IL-1β is a proinflammatory cytokine and triggers pronounced systemic inflammation [1].

To date, the spectrum of autoinflammatory syndromes continues to expand. The classical signaling pathway of inflammasome activation has been extended by many other pathophysiological mechanisms. The excessive activation of PRRs, for example, can lead to an increased expression and secretion of the pro-inflammatory cytokines IL-36, interferon α (IFNα), interferon γ (IFNγ) and tumor necrosis factor alpha (TNFα) via various signaling pathways, which in turn can result in different autoinflammatory diseases (Figure 1).

Chronic and excessive activation of innate immune receptors leads to auto-inflammation.

The activation of innate immunity is usually self-limiting in healthy individuals. However, chronic and excessive activation of the PRRs over a longer period of time due to mutations and dysregulation can lead to auto-inflammation [2].

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd.

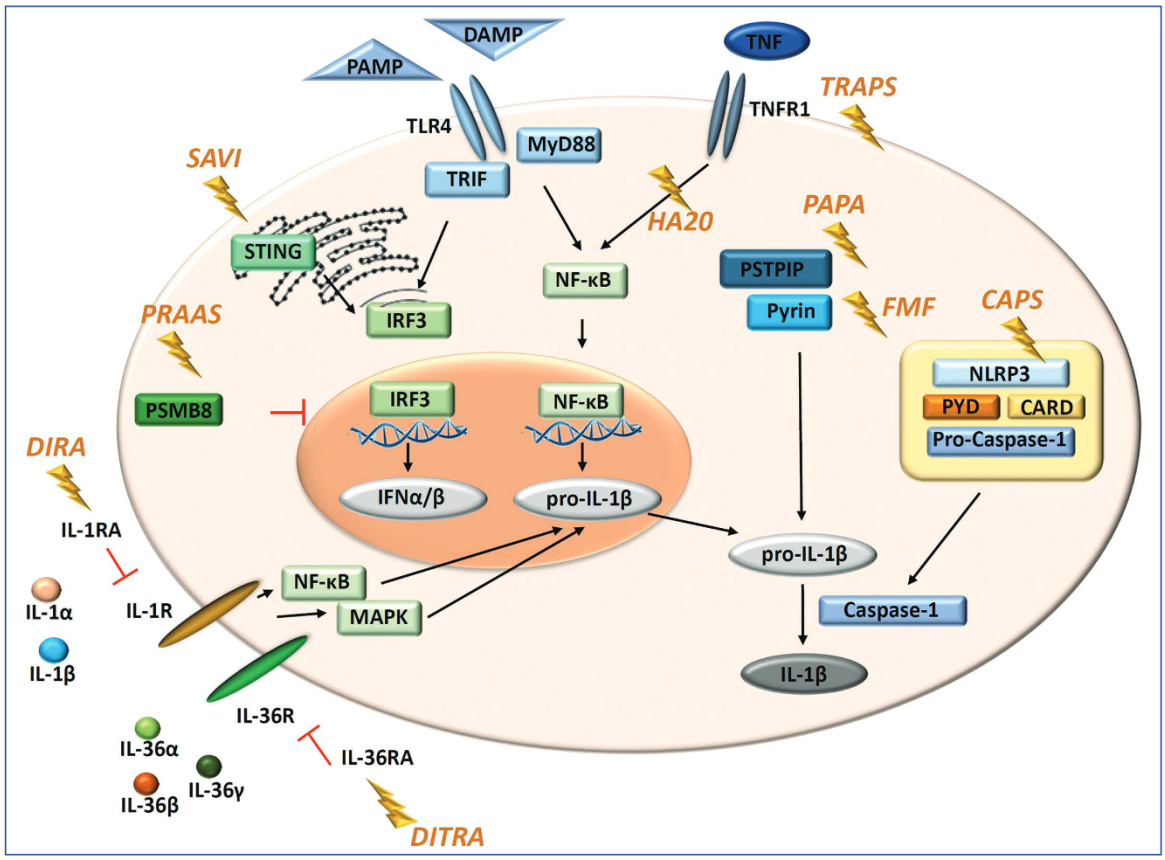

Figure 1 Signaling pathways of autoinflammatory syndromes in the cell.
Abbr.: CAPS, cryopyrin associated periodic syndrome; CARD, caspase recruiting domain; DIRA, deficiency of the IL-1 receptor antagonist; DITRA, deficiency of the IL-36 receptor antagonist; FMF, familial Mediterranean fever; HA20, A20 haploinsufficiency; IFNα/β, interferon alpha/beta; IL-1R, IL-1 receptor; IL-1RA, IL-1 receptor antagonist; IL-36R, IL-36 receptor; IL-36RA, IL-36 receptor antagonist; NF-κB, nuclear factor 'kappa-light-chain-enhancer' of activated B-cells; PAPA, pyogenic arthritis with pyoderma gangrenosum and acne; PAMP pathogen-associated molecular pattern; PRAAS, proteasome-associated auto-inflammatory syndromes; PSMB8, proteasome 20S subunit beta 8; PSTPIP1, proline serine threonine phosphatase interacting protein 1; PYD, pyrin domain; SAVI, STING-associated vasculopathy with onset in infancy; STING, stimulator of interferon genes; TLR, toll like receptor; TNF, tumor necrosis factor; TNFR1, TNF receptor 1; TRAPS, tumor necrosis factor-receptor-associated periodic syndrome; TRIF, TIR-domain-containing adapter-inducing Interferon-β.

Definition and classification of autoinflammatory syndromes

The term autoinflammatory syndromes originally referred to hereditary periodic fever syndromes, which initially only included the familial Mediterranean fever (FMF) and tumor necrosis factor-receptor-associated periodic syndrome (TRAPS), and was extended by the hyper-IgD syndrome (HIDS), the cryopyrin-associated periodic syndromes (CAPS), and later the PFAPA syndrome (periodic fever with aphthous stomatitis, pharyngitis and adenitis). Over time, many other diseases that do not count as fever syndromes were added to the group of autoinflammatory diseases.

Autoinflammatory syndromes can be classified according to various criteria. Even though the majority of the diseases are hereditary, also acquired

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd. | JDDG | 1610-0379/2021/1903

autoinflammation seems to play a role, for which reason we make a distinction between these. For the hereditary diseases, we distinguish between monogenic and polygenic autoinflammatory syndromes according to the mode of inheritance. Monogenic syndromes are diseases that are caused by a defect in a single gene (= mono-gene). This includes the majority of classic autoinflammatory diseases. The polygenic autoinflammatory diseases have a more complex inheritance pattern and include diseases such as Behçet's disease, Crohn's disease, gout, atherosclerosis and type 2 diabetes. The latter are not discussed in more detail in this article. Acquired autoinflammatory syndromes primarily include the Schnitzler syndrome, however acquired autoinflammation seems to also plays an important role in the development of the classical neutrophilic dermatoses like the Sweet syndrome and pyoderma gangrenosum.

A more precise and up-to-date classification of the autoinflammatory syndromes follows the pathophysiological mechanisms. The largest group is represented by the IL-1-mediated syndromes. Furthermore, there is a division into IL-36 and TNF-mediated diseases, nuclear factor-kappa B (NF-κB) mediated syndromes and interferon-mediated diseases (Table 1).

In this review article, we aim to build an understanding of the various forms of autoinflammation and of the important autoinflammatory diseases, in particular focus on the monogenic diseases. The classification is based on pathophysiological aspects. Moreover, new aspects of autoinflammation will be discussed.

IL-1 mediated diseases

Hereditary periodic fever syndromes (monogenic)

Cryopyrin-associated periodic syndromes (CAPS)

The cryopyrin-associated periodic syndromes (CAPS) are a group of rare disease patterns that are caused by mutations in the *NRLP3* (cryopyrin) gene [3, 4]. Mutations in *NLRP3* lead to a constitutive activation of caspase-1 and consequently an uncontrolled and excessive secretion of the pro-inflammatory cytokine interleukin-1β. The cryopyrin-associated periodic syndromes include:

- familial cold autoinflammatory syndrome (FCAS) (MIM #120100) [5],
- Muckle-Wells syndrome (MWS) (MIM #191900) [6],
- chronic infantile neurological cutaneous articular syndrome (CINCA), also known as neonatal-onset multisystemic inflammatory disease (NOMID) (MIM #607115) [7].

The inheritance pattern is autosomal dominant in FCAS and MWS, patients with CINCA mostly show sporadic mutations.

Clinical manifestations

The most common symptoms in all three syndromes are urticarial skin changes. They appear similar to normal urticaria, but in contrast to the latter are rather macular with an anemic margin on closer examination. Moreover, they hardly cause pruritus, persist for > 24 hours and do not respond well to antihistamines. Histology shows a neutrophile urticarial dermatositis (NUD), which is characterized by a neutrophil-rich, perivascular and interstitial-dermal infiltrate with leukocytoclasia without fibrinoid degeneration of vessel walls or dermal edema [8].

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd.

Table 1 Autoinflammatory Syndromes.

Pathomechanism		Disease	Gen	Inheritance	Involved organs	Skin symptoms
IL-1-mediated	Hereditary fever syndromes (monogenic)	CAPS FCAS (MIM #120100) MWS (MIM #191900) CINCA (MIM #607115)	*NLRP3*	AD AD *De novo*	Skin, joints, eyes Skin, joints, eyes, inner ear, bones, meninges Skin, joints, eyes, inner ear, bones, meninges, lymphadenopathy	Urticarial exanthema
		FMF (MIM #249100)	*MEFV*	AR	Skin, joints, pleura, peritoneum	Erysipelas-like lesions
		HIDS (MIM #260920)	*MVK*	AR	Skin, mucous membrane, eyes, joints, lymphadenopathy	Maculopapular exanthema, urticaria, petechiae
		PFAPA (MIM #142680)	–	–	Mucous membrane (stomatitis, pharyngitis), lymphadenopathy	Usually none
	Monogenic diseases	DIRA (MIM #612852)	*IL1RN*	AR	Skin, mucous membrane, bones/joints, rarely lungs	Pustular exanthema, nail changes, enoral mucous membrane lesions
		Majeed syndrome (MIM #609628)	*LPIN2*	AR	Skin, bone, periosteum, blood	Sweet syndrome-like lesions, erythematous plaques, pustular skin changes
		PAPA (MIM #604416)	*PSTPIP1*	AD	Skin, joints	Pyoderma gangrenosum, nodulocystic acne
	Polygenic/acquired diseases	SAPHO	–	–	Skin, bones, joints	Palmoplantar pustulosis, acne conglobata or fulminans, hidradenitis suppurativa, pyoderma gangrenosum, rarely Sweet syndrome
		Schnitzler syndrome	*Polygenic / NLRP3*	*De novo*	Skin, bones, joints, blood	Urticarial exanthema
		PAPASH	*PSTPIP1*	Not known	Skin, joints	Acne, pyoderma gangrenosum, hidradenitis suppurativa
		PASH	*PSTPIP1, MEFV, NOD2, IL1RN, PSMB8*	Not known	Skin	Acne, pyoderma gangrenosum, hidradenitis suppurativa

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd. | JDDG | 1610-0379/2021/1903

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd. | JDDG | 1610-0379/2021/1903

Table 1 Continued.

Pathomechanism	Disease	Gen	Inheritance	Involved organs	Skin symptoms
IL-36 -mediated	DITRA (MIM #614204)	*IL36RN*	AR	Skin	Generalized, pustular exanthema
NF-kB -mediated	BS (MIM # 186580) /EOS (MIM # 609464)	*NOD2 / CARD15*	AD *De novo*	Skin, eyes, joints	Granulomatous dermatitis
	CAMPS (MIM #602723)	*CARD14*	AD	Skin	Psoriasis vulgaris or pustulosa
	ORAS (MIM #617099)	*OTULIN*	AR	Skin, fatty tissue, joints, gastrointestinal tract	Pustular exanthema, panniculitis
TNFα -mediated	HA20 (MIM #616744)	*TNFAIP3*	AD	Skin, mucous membrane, eyes, joints, vessels, gastrointestinal tract	Erythema nodosum, erythematous papules, pseudofolliculitis, positive pathergy phenomenon
	TRAPS (MIM # 142680)	*TNFRSF1A*	AD	Skin, eyes, joints, pleura, periosteum	Painful urticarial exanthema, periorbital edema
Interferon-mediated	DADA2 (MIM # 615688)	*CECR1*	AR	Skin, joints, vessels, gastrointestinal tract, kidneys	Livedo reticularis or livedo racemosa, pustular exanthema
	PLCG2 associated syndromes (MIM # 614468)	*PLCG2*	AD	Skin, joints, eyes, gastrointestinal tract	Cold urticaria, granulomatous dermatitis
	PRAAS (MIM # 256040)	*PSMB8*	AR	Skin, joints, lymph nodes, muscles, brain	Pernio-like, nodular skin changes
	SAVI (MIM # 615934)	*TMEM173*	AD	Skin, joints, lungs, vessels	Violet, atrophic plaques on the hands, cold-induced ulcerations and livid nodules on nose, ear and cheeks

Abbr.. BS/EOS, Blau syndrome/early onset sarcoidosis; CAPS, cryopyrin associated periodic syndrome; CAMPS, CARD14-mediated psoriasis; DADA2, deficiency of adenosine deaminase 2; DIRA, deficiency of the IL-1 receptor antagonist; DITRA, deficiency of the IL-36 receptor antagonist; FMF, familial Mediterranean fever; HA20, A20 haploinsufficiency; HIDS, hyper IgD syndrome; ORAS, OTULIN-related autoinflammatory syndrome; PAPA, pyogenic arthritis with pyoderma gangrenosum and acne; PASH, pyoderma gangrenosum, acne and hidradenitis suppurativa; PAPASH, pyogenic arthritis, acne, pyoderma gangrenosum and hidradenitis suppurativa; PRAAS, proteasome-associated auto-inflammatory syndromes; SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis; SAVI, STING-associated vasculopathy with onset in infancy; TRAPS, tumor necrosis factor-receptor-associated periodic syndrome

The mildest form of CAPS is FCAS, which usually begins in infancy or early childhood. In addition to urticarial rashes, patients suffer from fever, headache, arthralgia and conjunctivitis, which usually occur 1–2 hours after exposure to cold and last up to 24 hours [9].

The onset of MWS is shortly after birth, but some symptoms appear later in adulthood. The syndrome is characterized by the clinical triad:

- periodic attacks of fever with urticarial skin lesions, arthralgia and headache,
- sensoneurinal hearing loss,
- secondary amyloidosis with nephropathy [10].

The most severe form of CAPS is CINCA/NOMID. Like FCAS, symptoms start already after birth and include maculopapular or urticarial rashes, fever, lymphadenopathy, hepatosplenomegaly and aseptic meningitis with mental retardation. In about 50 % of cases an arthropathy develops, which can be very difficult to handle and lead to malformations [11, 12].

Diagnosis

The diagnosis of CAPS is based on clinical and laboratory findings. An international team of experts used correspondence analysis of 284 cases and 837 controls to analyze variables that were consistently associated with the diagnosis of CAPS ($p < 0.001$). Based on this, criteria for the diagnosis of CAPS were developed (sensitivity 81 %, specificity 94 %) [13]:

Increase in inflammation markers (C-reactive protein (CRP) / serum amyloid-A (SAA)) in the serum *plus* at least two of six typical clinical manifestations for CAPS [13]:

- urticarial skin lesions,
- cold/stress-inducible episodes,
- sensoneurinal hearing loss,
- musculoskeletal symptoms (arthralgia/arthritis/myalgia),
- chronic aseptic meningitis,
- skeletal deformities.

For further confirmation of the diagnosis, a genetic testing can be performed to detect mutations in the *NLRP3* gene as previously shown in a large number of cases [14].

Treatment

Blocking interleukin-1 for the treatment of CAPS has been shown to be very effective. The human interleukin-1 receptor antagonist Anakinra (Kineret®) [15, 16] and the monoclonal antibody against IL-1β canakinumab (Ilaris®) showed good responses [17, 18]. Rilonacept – a dimeric fusion protein that binds to IL-1β – also represents a good option for therapy [19–21]. However, it was withdrawn from the European market.

Familial Mediterranean fever (FMF) (MIM #249100)

Familial Mediterranean fever is an autosomal recessive disease, which occurs primarily in patients of Turkish, Armenian, Arabic and Sephardic-Jewish origin in the Mediterranean region. The affected gene is *MEFV*, which codes for the protein

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd. | JDDG | 1610-0379/2021/1903

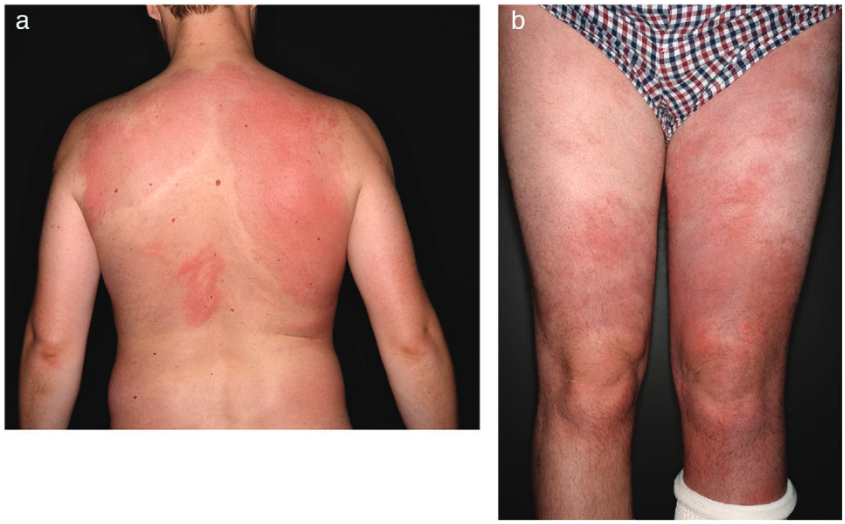

Figure 2 Familial Mediterranean fever. Erysipelas-like erythema on the back (a) and on the legs (b) of a patient suffering from familial Mediterranean fever.

pyrine. Pyrine can form an inflammasome together with adapter proteins and thereby lead to activation and secretion of IL-1β [22, 23].

Clinical manifestations

The familial Mediterranean fever manifests itself as erysipelas-like skin changes.

The patients suffer from recurrent attacks of fever, which last for about 1–3 days. The frequency of the relapses is very different and ranges from once a week to once every few months. Fever is often the only symptom in children under the age of 2 [24]. In children aged 5 and above, the fever is accompanied by erysipelas-like skin changes (Figure 2), synovitis, pleuritis and peritonitis [25, 26]. The latter become manifest in pain in the abdomen, thorax and joints. In the course of the disease, secondary amyloidosis can develop, which can lead to renal insufficiency [27].

Treatment

A well-established therapy for FMF is colchicine, which has a good effect in reducing relapses and basal inflammatory activity, as well as in preventing late effects such as amyloidosis [28]. In the event of side effects or contraindications to colchicine, IL-1 inhibitors can be used as second-line therapy.

Hyper IgD syndrome (HIDS) (MIM #260920)

HIDS is a rare, autosomal recessive disease that is caused by mutations in the *MVK* gene (coding for the mevalonate kinase). *MVK* mutations lead to a reduced activity of the enzyme, which in turn leads to an increased production of IL-1β via complex processes. Although HIDS can occur worldwide, an increased incidence has been registered in Northern France and the Netherlands [29, 30].

Clinical manifestations

Symptoms usually begin in infancy (before the age of 5) and are manifested by severe febrile episodes with cervical lymphadenopathy, joint pain and skin rashes.

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd.

Patients also suffer from abdominal pain, diarrhea and vomiting. The flare-ups occur about every 4–8 weeks and last for 3–7 days. Skin involvement is non-specific and includes maculopapular or urticarial skin lesions, or petechiae. Half of the patients also suffer from oral aphthae. The disease usually runs without serious complications [31, 32].

Diagnosis

The typical clinical picture with recurrent febrile episodes and oral aphthae is completed by blood laboratory tests which present increased CRP and leukocytosis. In addition to these non-specific signs of inflammation, elevated IgD levels in the serum are characteristic, which can be detected in about 80 % of the patients. In addition, IgA levels turned out to be increased. Histology shows unspecific perivascular infiltrates with few neutrophils. Genetic testing proofs the diagnosis [33].

Elevated IgD levels are detectable in the majority of HIDS patients.

Treatment

No specific therapy exists for HIDS. Symptoms during relapses can be relieved by using non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. More and more, biologics such as etanercept (anti-TNF fusion protein), anakinra or canakinumab are being used, with the most convincing data available for canakinumab [33, 34].

Monogenic diseases

Deficiency of the IL-1 receptor antagonist (DIRA) (MIM #612852)

DIRA is a rare, autosomal recessive inherited disorder caused by mutations in the IL1RN gene. These are so-called “founder mutations”, which represent genetic deviations of an isolated population. Accordingly, there is a particular geographical distribution with frequent occurrence in Newfoundland, Puerto Rico and Holland. Mutations in IL1RN lead to an absence or dysfunction of the IL-1 receptor antagonist (IL-1Ra). As a result, IL-1 cannot be antagonized, thereby leading to excessive stimulation by IL-1 cytokines and systemic inflammation [35, 36].

Clinical manifestations

The symptoms begin right after up to a few months after birth. In contrast to other autoinflammatory syndromes, patients usually do not show episodes of high fever. Patients develop pustular rashes, ranging from discrete isolated pustules to generalized exanthema. Other symptoms include nail changes such as pits or onychomadesis and oral mucosal lesions in the early years of life. Furthermore, patients suffer from inflammation in the joints with pronounced swelling. The disease can lead to complications early on and many babies have a failure to thrive. If the disease is not detected and treated early enough, it can lead to a dramatic course of disease with the development of severe systemic inflammation (SIRS), multi-organ failure and death [35].

Delayed therapy can lead to severe courses of disease with SIRS, multi-organ failure and death in DIRA patients.

Diagnosis

The diagnosis is based on the typical clinical, histologic and radiological findings and genetic analysis. Infections must be ruled out. The histology shows intraepidermal pustules and a neutrophil infiltrate and edema in the dermis, but is not specific for DIRA.

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd. | JDDG | 1610-0379/2021/1903

The X-ray shows pronounced ballooning and deformities of long bones. The diagnosis can only be confirmed by the genetic detection of a mutation in IL1RN [35, 37].

Treatment

The missing protein has to be replaced for a lifetime. The recombinant IL1R antagonist Anakinra is suitable for this [35, 38, 39].

Majeed syndrome (MIM #609628)

Majeed syndrome is a rare autosomal recessive disorder that has been diagnosed in only a few families in the Middle East so far. The syndrome is caused by mutations in the *LPIN2* gene, which abrogates the enzymatic activity of Lipin-2. How exactly the loss of function of Lipin-2 leads to the clinical manifestations of Majeed syndrome is unknown. However, it is believed that IL-1RA production is reduced [40].

Clinical manifestations

Majeed syndrome patients show a triad of recurrent multifocal osteomyelitis, congenital anemia and neutrophilic dermatosis.

The characteristic clinical picture is a triad of chronic recurring multifocal osteomyelitis, congenital anemia and neutrophil dermatosis. Already during infancy or early childhood, children suffer from recurrent episodes of pain and joint swelling that persist into adolescence and can lead to joint contractures, muscle atrophy and short stature. During the first year of life, patients present with a hypochromic, microcystic anemia, which can be either mild or lead to the need for transfusion. The skin of patients with Majeed syndrome is also affected: Patients often develop a neutrophilic dermatosis, which is clinically and histologically similar to a Sweet syndrome. Furthermore, Majeed patients can develop erythematous plaques, psoriasis and pustular skin changes.

Diagnosis

If typical clinical manifestations exist, imaging should be performed, which usually shows osteolysis with surrounding sclerosis. Moreover, it is important to perform bone biopsies to rule out infectious osteomyelitis. Evidence of *LPIN2* mutations in genetic testing confirms the diagnosis.

Treatment

Symptoms can be treated with NSAIDs or corticosteroids. Transfusion is indicated for severe anemia. The Neutrophil dermatosis responds very well to steroid therapy. As long-term therapy, biological therapies proved to be effective. TNFα antagonists showed good results, but even better data are available for the IL-1 antagonists anakinra and canakinumab [40–42].

Pyogenic arthritis with pyoderma gangrenosum and acne (PAPA) syndrome (MIM #604416)

PAPA syndrome is a rare inheritable disorder caused by an autosomal dominant mutation in the *PSTPIP1* gene [43]. The gene product of *PSTPIP1* binds to pyrin, which activates the inflammasome and thereby the production of active interleukin-1β [44].

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd.

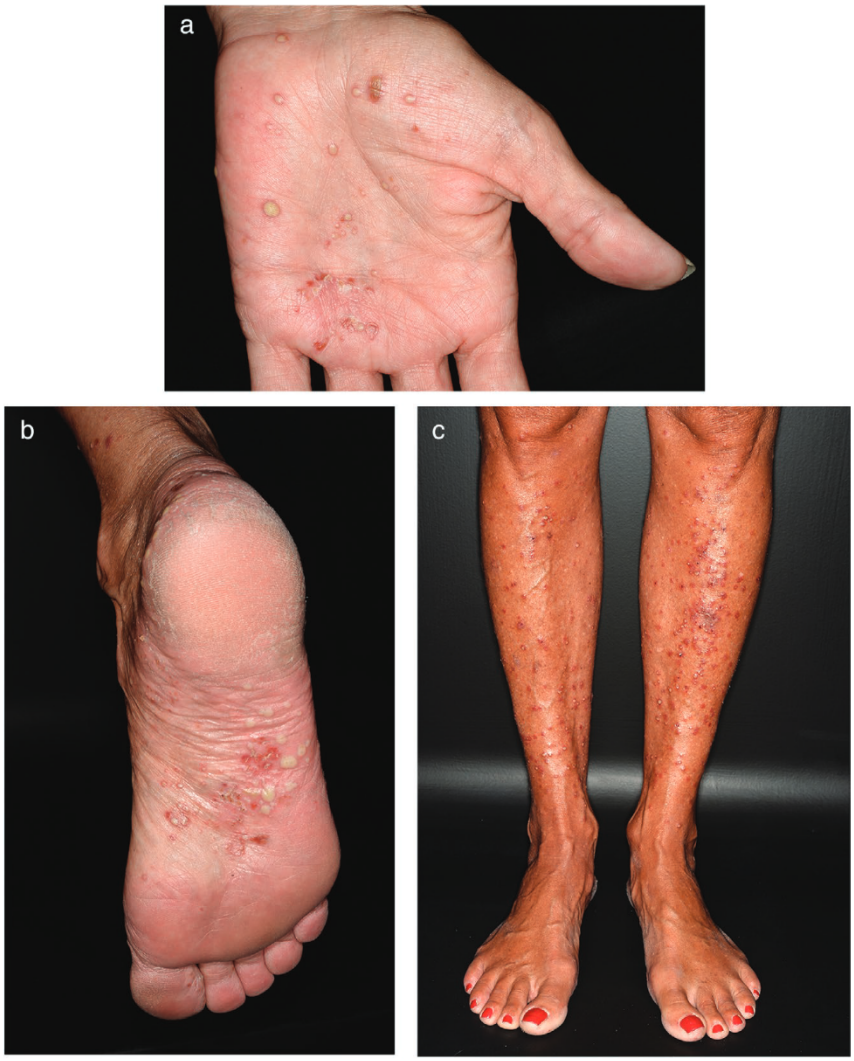

Figure 3 SAPHO syndrome. Palmoplantar pustulosis (a, b) and pustular exanthema on the lower legs (c) of a patient suffering from SAPHO syndrome (SAPHO: synovitis, acne, pustulosis, hyperostosis, osteitis).

Clinical manifestations

Symptoms include sterile arthritis, pyoderma gangrenosum, and acne. Arthritis usually appears as the first symptom, and a massive infiltration of neutrophil granulocytes in the large joints can be determined. At puberty, patients develop skin symptoms including pyoderma gangrenosum and severe nodulocystic acne [44] (Figure 3).

Diagnosis

The diagnosis is based on the typical clinical symptoms. Moreover, increased acute phase proteins as well as increased amounts of interleukin-1β and TNFα can be detected in the laboratory. The detection of mutations in the PSTPIP1 gene by genetic testing proves the diagnosis [45].

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd. | JDDG | 1610-0379/2021/1903

Treatment

Arthritis flare-ups can be treated well with intra-articular steroid infiltration. The response of skin changes to therapy is diverging; treatment with TNFα antagonists such as infliximab or etanercept [46, 47] and the interleukin-1 receptor antagonist Anakinra [48, 49] have been described as effective.

Variants

The clinical triad of pyoderma gangrenosum, acne and hidradenitis suppurativa (PASH) has been recently defined as an autoinflammatory syndrome and differs from PAPA syndrome by the lack of pyogenic arthritis [50]. In addition, the syndrome with the constellation of symptoms pyogenic arthritis, acne, pyoderma gangrenosum and hidradenitis suppurativa (PAPASH) has been described [51]. In both diseases, mutations in the *PSTPIP* gene were detected in some cases, in PASH also mutations in *MEFV*, *NOD2*, *IL1RN* and *PSMB8* have been described [52].

Polygenic/acquired diseases

Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis (SAPHO) syndrome

SAPHO syndrome is one of the most common autoinflammatory syndromes with an incidence of 1 in 10,000 in Caucasians [53, 54]. The origin of disease is multifactorial and seems to combine genetic, immunological, as well as environmental aspects. The role of IL-1 has been reported in several cases [55, 56], as well as an increased incidence of the HLA-B27 antigen in the blood [53].

Clinical manifestations

The symptoms can occur in all age groups and are usually chronic and appear in episodes. The typical features of SAPHO syndrome are neutrophilic skin changes and osteo-articular manifestations. The skin changes most often present as palmoplantar pustulosis (Figure 4), furthermore they can manifest themselves as acne conglobata or fulminans, hidradenitis suppurativa, pyoderma gangrenosum and infrequently as Sweet syndrome. Rarely, psoriasis vulgaris or pustulosa can occur [57]. The involvement of the bones and joints manifests as painful osteitis of the sternum, clavicles and ribs, as synovitis, hyperostosis and as oligoarthritis. The osteoarticular symptoms can lead to long-term restriction of mobility, however the disease has a good prognosis overall [58].

SAPHO syndrome patients can develop a multitude of neutrophilic skin changes.

Diagnosis

The diagnosis of SAPHO syndrome is challenging. It is based on clinical, histological and radiological findings. Like the clinical skin symptoms, the histology is variable. Imaging ranges from conventional X-rays, CT, MRI to bone scintigraphy. At the beginning of the disease, biopsies of the affected bones show abscesses, a so-called sterile osteomyelitis. Over time, bone marrow fibrosis and sclerotic trabeculae develop [54].

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd.

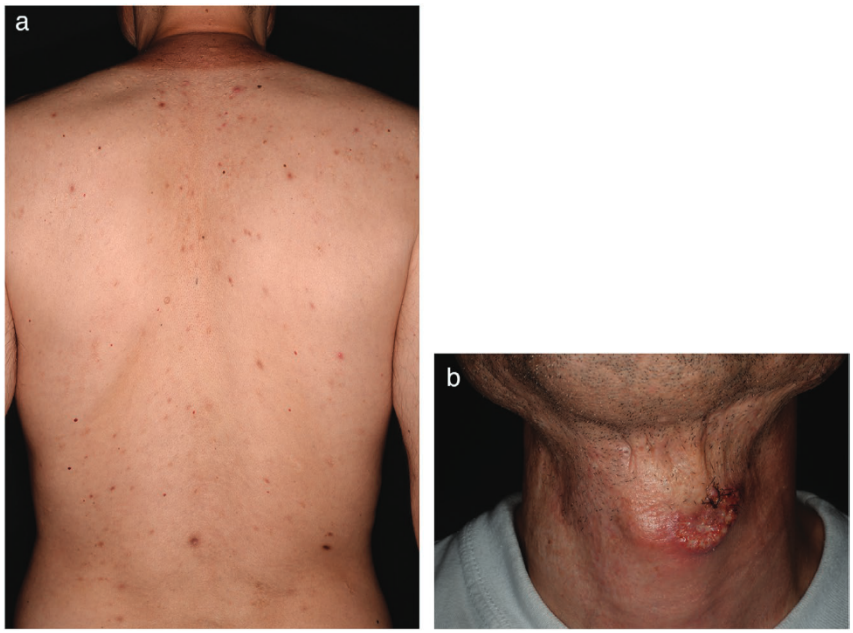

Figure 4 PAPA syndrome. Nodulocystic acne on the back (a) and pyoderma gangrenosum in the area of acne scars on the neck of a patient suffering from PAPA syndrome (PAPA, pyogenic arthritis with pyoderma gangrenosum and acne).

Treatment

To date, the treatment of SAPHO syndrome is largely symptomatic. In most cases, non-steroidal analgesics are used as first-line treatment. In addition, corticosteroids can be administered intralesionally and systemically. Conventional immunosuppressants such as methotrexate, sulfasalazine, or azathioprine and colchicine [59] have also been used therapeutically [60]. Osteomyelitis responds well to bisphosphonates [61]. In refractory cases, TNFα antagonists such as infliximab have shown good results [62]. The response to Anakinra was also promising [56, 59]. Skin symptoms such as palmoplantar pustulosis or pustular psoriasis respond well to topical steroids and PUVA therapy.

Schnitzler syndrome

Schnitzler syndrome is a rare disease with a late onset. Several hundreds of cases have already been reported worldwide. It is considered as a sporadic acquired autoinflammatory disorder, but in some patients a mosaicism of *NLRP3* mutations in myeloid cells has been demonstrated [63].

Clinical manifestations

The Schnitzler syndrome usually begins in the second half of life and takes a chronic course. In most cases, the symptoms begin with mildly itchy, recurrent urticaria. The frequency of the relapses varies greatly from patient to patient. In contrast to classic urticaria, the response to antihistamines is low. Histologically, a neutrophilic infiltrate in the dermis with no signs of vasculitis can be recognized. Another typical symptom is intermittent fever, and some patients also develop lymphadenopathy and hepatomegaly. Many patients also suffer from arthralgia

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd. | JDDG | 1610-0379/2021/1903

and bone pain, in particular in the pelvic bone and tibia [64]. In the course of the disease, amyloidosis can develop, which can lead to serious complications. 85–100 % of patients with Schnitzler syndrome develop a monoclonal gammopathy, usually of the IgM type (IgMκ), which is very characteristic for the disease. 10–20 % of patients develop a lymphoproliferative disease such as Waldenström's disease or B cell lymphoma by marginal zone lymphoma [64].

85–100 % of all Schnitzler syndrome patients develop a monoclonal gammopathy.

Diagnosis

The diagnosis of Schnitzler syndrome is based on clinical, laboratory and radiological findings. The skin lesions help in making the diagnosis and manifest themselves as recurrent NUD with urticarial skin changes. The latter differ in their macular aspect and anemic margin from normal urticaria. Also histology shows the picture of a NUD [8]. In addition, patients suffer from episodes of fever and joint and bone pain, particularly in in the pelvic bone and tibia [64]. Moreover, elevated CRP, leukocytosis (usually neutrophilia) and sometimes mild anemia can be demonstrated. An additional IgM gammopathy is very suggestive for Schnitzler syndrome. Genetic tests are not carried out by default as no causative or predisposing genes have been identified in Schnitzler syndrome [64].

Treatment

Non-steroidal anti-inflammatory drugs and corticosteroids can relieve fever, arthralgia and bone pain. Urticarial skin changes, on the other hand, do not respond well to antihistamines. Colchicine is an established treatment for Schnitzler syndrome, however therapy response is not sufficient in every patient. Complete remission can be achieved in 90 % of the patients by antagonizing IL-1; both anakinra and canakinumab represent good treatment options [8, 64–66].

Pyoderma gangrenosum, acne and hidradenitis suppurativa (PASH) and pyogenic arthritis, acne, pyoderma gangrenosum and hidradenitis suppurativa (PAPASH).

The two syndromes were described in the chapter "Pyogenic arthritis with pyoderma gangrenosum and acne (PAPA) syndrome" as variants of the PAPA syndrome.

IL-36 mediated diseases

Deficiency of the IL-36 receptor antagonist (DITRA) (MIM #614204)

DITRA is an autosomal recessive inherited syndrome caused by mutations in the *IL36RN* gene. This loss-of-function mutation creates a defective protein of the receptor antagonist of all three isoforms of IL-36, which leads to excessive stimulation by the receptor agonists. This in turn leads to a strong secretion of IL-8, which in turn acts as a potent neutrophil attractor.

A defective IL-36 receptor antagonist is causing a strong neutrophilic inflammation via IL-8 secretion.

Clinical manifestations

The disease usually begins in childhood and is characterized by recurrent episodes of a generalized, pustular rash with fever, blood neutrophilia and increased

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd. | JDDG | 1610-0379/2021/1903

acute phase proteins. In addition to the skin, the nails are also affected and show pronounced dystrophies. Joints are usually not involved. The frequency of relapses varies from patient to patient and is triggered by medication, infections, pregnancy, menstruation and discontinuation of systemic steroids.

Diagnosis

If typical clinical symptoms and histology with neutrophil-rich inflammation exist, a genetic testing for the presence of *IL36RN* mutations should be carried out.

Treatment

Targeted therapy with a monoclonal IL-36 receptor antibody is under development and is currently being tested in advanced human clinical studies. A phase 1 clinical trial showed promising results [67]. Currently IL-1 or IL-17 antagonists are being used for treatment and have shown good responses [68, 69].

NF-κB mediated diseases

Blau syndrome (BS) (MIM # 186580)/early onset sarcoidosis (EOS) (MIM #609464)

Blau syndrome is an autosomal dominant inherited or sporadic disease caused by a mutation in the *NOD2/CARD15* gene. *NOD2/CARD15* belongs to the family of intracellular receptors that bind bacterial peptidoglycans. Mutations in *NOD2/CARD15* causes constitutive stimulation of the NOD2 receptor, which leads to an excessive activation of NF-κB and thus leads to a persistent inflammatory state [70].

Clinical manifestations

Blau syndrome patients develop granulomatous dermatitis, polyarthritis, bilateral granulomatous iridocyclitis and uveitis.

The first symptoms occur during early childhood and usually begin as granulomatous dermatitis. Patients develop yellowish-brown, flat, partially scaly papules in the area of the trunk and extremities [70, 71]. The majority of patients also suffer from chronic polyarthritis, which manifests itself as painless intra-articular synovitis and polyarthritis [72]. Moreover, patients develop bilateral granulomatous iridocyclitis and uveitis, of which the latter can cause loss of vision, photophobia and pain. The uveitis is difficult to treat and is the symptom with the highest rate of complications and long-term consequences.

Diagnosis

If clinically suspected, biopsies of the skin, joints and/or eyes should be performed. Histology reveals non-caseating granulomas with PAS-positive histiocytes and giant cells in the dermis. Diagnosis can be confirmed by genetic testing for *NOD2* mutations [72].

Treatment

The treatment remains challenging. Systemic corticosteroids are used frequently, as well as immunosuppressants such as cyclosporin or methotrexate. Inhibition of IL-1 showed variable response [73]. The best data so far exist for TNFα inhibitors, in particular for adalimumab [70, 74–76].

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd. | JDDG | 1610-0379/2021/1903

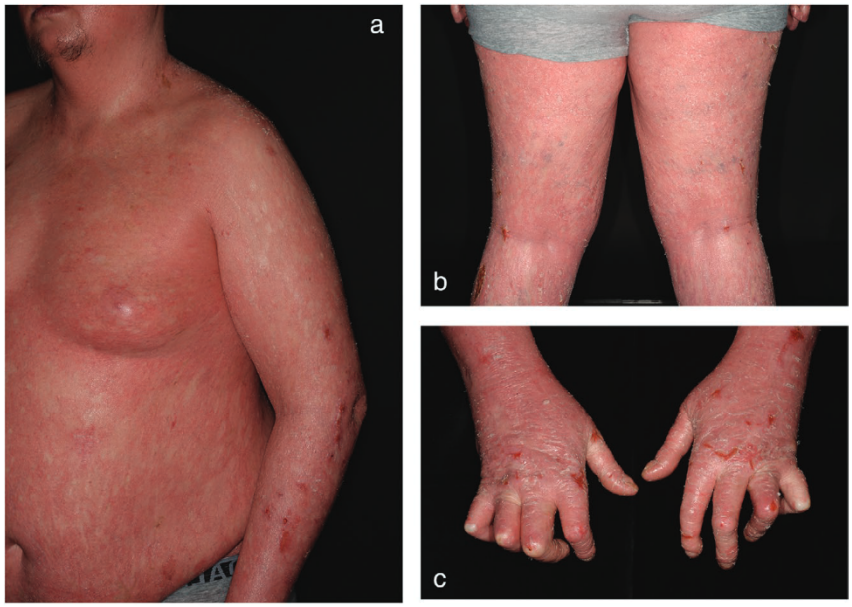

Figure 5 CAMPS. Severe erythrodermic psoriasis (a, b) with arthritis of the hands (c) of a patient suffering from CAMPS (CARD14-mediated psoriasis).

CARD14 mediated psoriasis (CAMPS)/familial psoriasis (PSORS2) (MIM #602723)

CAMPS is an autosomal dominant disease that clinically corresponds to psoriasis. Affected patients carry so-called gain of function mutations in the *CARD14* gene, which leads to an increased activity of the nuclear factor-kappa B (NF-κB) signaling pathway. This leads to an increased formation of pro-inflammatory cytokines such as IL-8, IL36γ and IL-1β [77, 78].

Clinical manifestations

Clinical findings are common psoriasis vulgaris or pustular psoriasis, as well as arthritis, however some cases show very severe courses of disease (Figure 5).

Diagnosis

In case of clusters in families, genetic testing should be initiated.

Treatment

In addition to topical measures including topical steroids and vitamin D3 analogues, ustekinumab, a p40 (IL12/IL23) antagonist, has been successfully used in certain cases [77, 78].

OTULIN-related autoinflammatory syndrome (ORAS) (MIM #617099)

ORAS is a very rare disease, only six cases have been reported in the literature so far. Causative is a mutation in the *OTULIN* gene, which leads to increased ubiquitination and activation of the NF-κB signaling pathway [79, 80].

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd.

Clinical manifestations

Affected patients suffer from severe systemic inflammation already during infancy. Symptoms are fever, arthralgia, skin rashes, lipodystrophy, diarrhea and delayed development. Skin changes include pustular rashes and panniculitis.

Diagnosis

Systemic inflammation with increased CRP and leukocytosis can be detected in the blood. A biopsy of the lesional skin should be performed, histology shows a neutrophil infiltrate and nodular panniculitis. Genetic studies can proof the diagnosis by the detection of *OTULIN* mutations.

Treatment

The majority of patients respond well to TNFα inhibitors. Steroids and IL-1 blockade were shown to be less effective [79, 80].

TNFα-mediated diseases

A20 haploinsufficiency (HA20) (MIM #616744)

HA20 is a rare autosomal-dominant disease, which is caused by a mutation in the *TNFAIP3* gene. *TNFAIP3* is coding for the enzyme TNFAIP3/A20, which is negatively regulating both the NF-κB-signaling pathway and the NLRP3 inflammasome. The mutation determines haploinsufficiency and is thereby leading to the dysfunction of the protein, which in turn is causing overproduction of NF-κB dependent proinflammatory cytokines [81, 82]. The clinical manifestations are not distinguishable from Behçet's disease (BD), therefore HA20 is ranked among the spectrum of BD [82–84].

Clinical manifestations

Symptoms start during childhood or adulthood and present like BD: Patients suffer from fever, bipolar aphthosis, polyarthritis and uveitis. Moreover, the affected persons can develop gastrointestinal ulcers, and cerebral and retinal vasculitis. Skin manifestations are diverse and range from nodal erythema, erythematous papules to pseudofolliculitis. Like in BD, the pathergy phenomenon is positive [81, 82, 84].

Diagnosis

The diagnosis is based on clinical findings and is confirmed by detection of genetic mutations in *TNFAIP3*. Additionally, unspecific autoimmune phenomena like antinuclear antibodies, anti-ribonuclear protein, anti-double-strand DNA and lupus anticoagulant are present [82].

Therapy

A good therapy response has been described for colchicine. Furthermore, TNFα inhibitors and the IL1RA Anakinra have been effective in some cases [2, 82, 85].

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd. | JDDG | 1610-0379/2021/1903

TNFα receptor associated periodic syndrome (TRAPS) (MIM # 142680)

TRAPS is one of the most frequent autoinflammatory syndromes.

The TNFα receptor-associated periodic syndrome is one of the most common autoinflammatory syndromes, and more than 1000 cases have been reported. The responsible gene *TNFRSF1A* codes for the TNF receptor1 (TNFR1), which is primarily responsible for TNF signaling. The stimulation of TNFR1 leads to either apoptosis through caspase activation or NF-κB-induced inflammation. However, the exact pathomechanism has not yet been fully clarified [86]. In this review article, the syndrome is listed under the TNFα-mediated diseases, however the exact classification of the disease is unclear as patients show a very good response to IL-1 blockade.

Clinical manifestations

Affected individuals usually contract the syndrome before the age of ten, but a small proportion shows the first symptoms later in life. Patients present with recurrent fever, which persists for several weeks. The frequency of the relapses varies greatly between the people affected. The episodes can be accompanied by abdominal pain, diarrhea and vomiting (sterile peritonitis), myalgia (fasciitis), arthralgia (serositis, arthritis) and conjunctivitis. Patients usually have severe skin infections with painful urticarial rashes, and periorbital edema represents a characteristic symptom. On the long-term, it can lead to the development of amyloidosis in around 10–15 %, which can lead to renal insufficiency due to the deposition of SAA in the kidney [87, 88].

Diagnosis

The clinical findings play a seminal role and should be complemented by laboratory and histological examinations. In the serum, an increase in the acute phase proteins and the TNFα can be displayed. Skin histology shows a mononuclear, perivascular infiltrate in the subcutaneous fascia with occasional panniculitis. The detection of mutations in *TNFRSF1A* by genetic testing is evidencing the diagnosis [87].

Treatment

NSAIDs and corticosteroids can be used to treat symptoms, but are not suitable for long-term treatment. Good responses to the TNFα blocker etanercept could be demonstrated, however in a few cases it also triggered severe flare-ups [89]. Recent studies report a very good therapeutic response to IL-1 blockade by anakinra and canakinumab [90, 91].

Interferon-mediated diseases

Deficiency of adenosine deaminase 2 (DADA2) (MIM # 615688)

Interferon-mediated diseases represent a new group of autoinflammatory syndromes.

DADA2 is a very rare autosomal recessive inheritable disorder with a heterogeneous clinical picture. The disease is caused by mutations in *CECR1*, which encodes the adenosine deaminase 2 (ADA2). Affected patients have a reduced enzyme activity of ADA2, which in turn limits the integrity of the vascular endothelia and leads

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd.

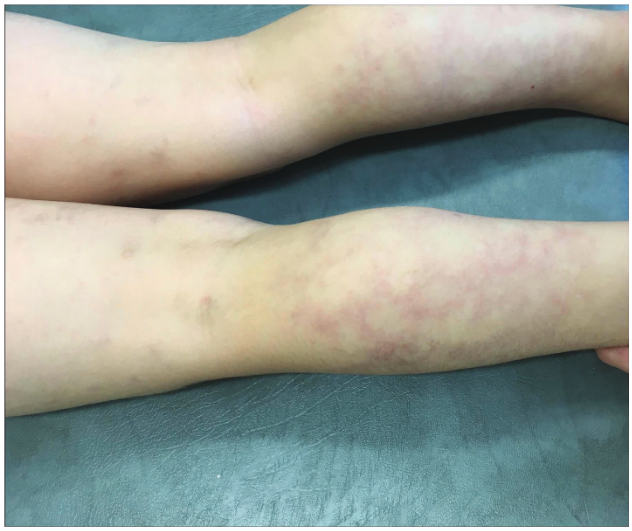

Figure 6 DADA2. Livedo racemosa on the legs of a 5 year old patient suffering from DADA2 syndrome (DADA2, deficiency of adenosine deaminase 2).

to the loss of neutrophil granulocytes [92]. In addition, a constitutively increased activity of type I interferons was found [93].

Clinical manifestations

The symptoms start in early childhood. The disease is characterized by recurrent episodes of systemic inflammation and various vasculopathies. The children suffer from fever attacks, and most of them have ischemic and hemorrhagic strokes before the age of 5. Livedo racemosa (Figure 6) is a very characteristic symptom of DADA2 and represents the skin sign of vasculitis in small and medium-sized vessels (polyarteritis nodosa), but many patients also show maculopapular rashes. Hepatosplenomegaly, recurrent bacterial infections, eye and musculoskeletal involvement are also variable symptoms [94].

Livedo racemosa is a typical symptom in DADA2 patients.

Diagnosis

The diagnosis is usually made years after the first symptoms appear. In addition to the typical clinical picture, there are increased inflammatory markers in the blood (CRP), lymphopenia, hypogammaglobulinemia and low IgM and IgA levels [94]. The histology of the skin shows inflammation of the small and medium-sized vessels, as usually found in polyarteritis nodosa. The proof of the diagnosis is being made by genetic testing, by which mutations in the *CECR1* gene can be detected.

Treatment

In order to prevent vascular complications such as strokes sufficiently, a strict immunosuppressive/-modulating treatment is required. Systemic steroids can provide relief, in particular during episodes of disease, and good results have also been achieved with TNFα inhibitors [95]. Moreover, case reports described hematopoietic stem cell transplants as a promising therapeutic approach [96].

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd. | JDDG | 1610-0379/2021/1903

Proteasome-associated auto-inflammatory syndromes (PRAAS) (MIM # 256040)

PRAAS is a group of rare autoinflammatory diseases, which are mostly caused by mutations in *PSMB8*. This term PRAAS includes several syndromes including chronic atypical neutrophil dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome, joint (joint) contractures, muscle atrophy, hepatomegaly, splenomegaly, microcystic anemia, and panniculitis-induced lipodystrophy (JMP) syndrome, the Japanese autogenous syndrome with lipodystrophy (JASL) and the Nakajo-Nishimura syndrome (NNS), which was first described in 1939. Mutations are inherited in an autosomal recessive manner and cause defective proteasome formation. This leads to cell stress and an excessive type I interferon signaling [97, 98].

Clinical manifestations

The symptoms start early in life and in most cases manifest before the age of one. The affected individuals develop fever and nodular skin changes, moreover they show joint involvement up to contractures, and lipodystrophy. In some cases, periorbital erythema, lymphadenopathy, hepatosplenomegaly, short stature, myositis, or calcification of the basal ganglia occur [97].

PRAAS patients develop nodular skin changes and a periorbital erythema.

Diagnosis

Elevated CRP and chronic anemia can be demonstrated in laboratory chemistry. Serologically, hypergammaglobulinemia and elevated IgG, IgE, IgA and IgM levels are detectable in some cases. In addition, autoantibodies are sometimes detectable. Biopsies of lesional skin should be performed; Histologically, a dense mixed cell infiltrates with histiocytes, eosinophilic and neutrophilic granulocytes in the dermis and subcutis can be demonstrated. If PRAAS is suspected, a genetic test should be carried out to confirm *PSMB8* mutations.

Treatment

The therapy of PRAAS is difficult and no long-term success has been achieved so far. Systemic steroids have a short-term effect on the skin changes, but not on the other symptoms. Immunosuppressants, as well as targeted antibody therapies including anti-TNFα antibodies, IL-1Ra (anakinra), IL-6Ra (tocilizumab) could not show sufficient effect. In contrast, the use of JAK inhibitors seems to be promising, as been reported in case reports [99].

STING-associated vasculopathy with onset in infancy (SAVI) (MIM # 615934)

SAVI is an autosomal dominant inheritable disorder caused by mutations in the *TMEM173* gene. *TMEM173* codes for the protein STING, which recognizes cytosolic DNA, activates IRF3 and thus induces the transcription of IFN [100].

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd.

Clinical manifestations

The symptoms begin in infancy and are characterized by recurrent episodes of fever, lung involvement and vasculitic skin changes. The latter manifest themselves as violet atrophic plaques on the hands, cold-induced ulcerations and lumps on the nose, ear and cheeks. Complications such as gangrene and septal perforation can occur [101].

Diagnosis

The typical clinical findings should be complemented by laboratory tests. High acute phase proteins and low titer autoantibodies (ANA, ANCA, antiphospholipid antibodies) can be detected [100, 102]. Histology shows vasculitis of the small and medium-sized vessels with dense neutrophil infiltrate and fibrinous microthrombi [102, 103].

Treatment

Blocking the IFN pathway with JAK inhibitors (baricitinib) has been shown to be effective. Other biologicals and conventional immunosuppressants, however, showed little effect [104].

Neutrophil dermatoses as a new entity of autoinflammatory diseases

Neutrophil dermatoses are a clinically heterogeneous group of diseases with dermal infiltrate of neutrophil granulocytes without the presence of pathogens. The main representatives of this group are pyoderma gangrenosum and Sweet syndrome. Interestingly, neutrophil skin changes are an important symptom of many autoinflammatory diseases. Both pyoderma gangrenosum and Sweet syndrome can be part of autoinflammatory syndromes such as PAPA or SAPHO syndrome. In both diseases, increased levels of IL-1β were found in the skin and in the circulation, which also in plays a key role in the majority of autoinflammatory syndromes [105, 106]. Therefore, the excessive activation of the innate immune system with increased production of IL-1 plays a central role both in classic autoinflammatory syndromes and neutrophil dermatoses. Based on these facts, autoinflammation is believed to be a major cause of neutrophil dermatoses [107–109].

Neutrophilic dermatoses are considered as new members of the group of autoinflammatory diseases.

The path to diagnosis – recommendations for the dermatological practice

Due to their rare occurrence, autoinflammatory syndromes are often not identified for a long period of time. Years of systemic inflammation, however, can lead to severe end organ damage such as amyloidosis with subsequent renal failure. For this reason, an early identification of affected patients is crucial. Since the skin is involved in a majority of autoinflammatory syndromes, the dermatologist plays a fundamental role in the detection of these diseases. Urticarial skin changes are considered the typical sign of skin involvement, however almost all primary efflorescences are possible (Figure 7). For this reason, an examination solely of the

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd. | JDDG | 1610-0379/2021/1903

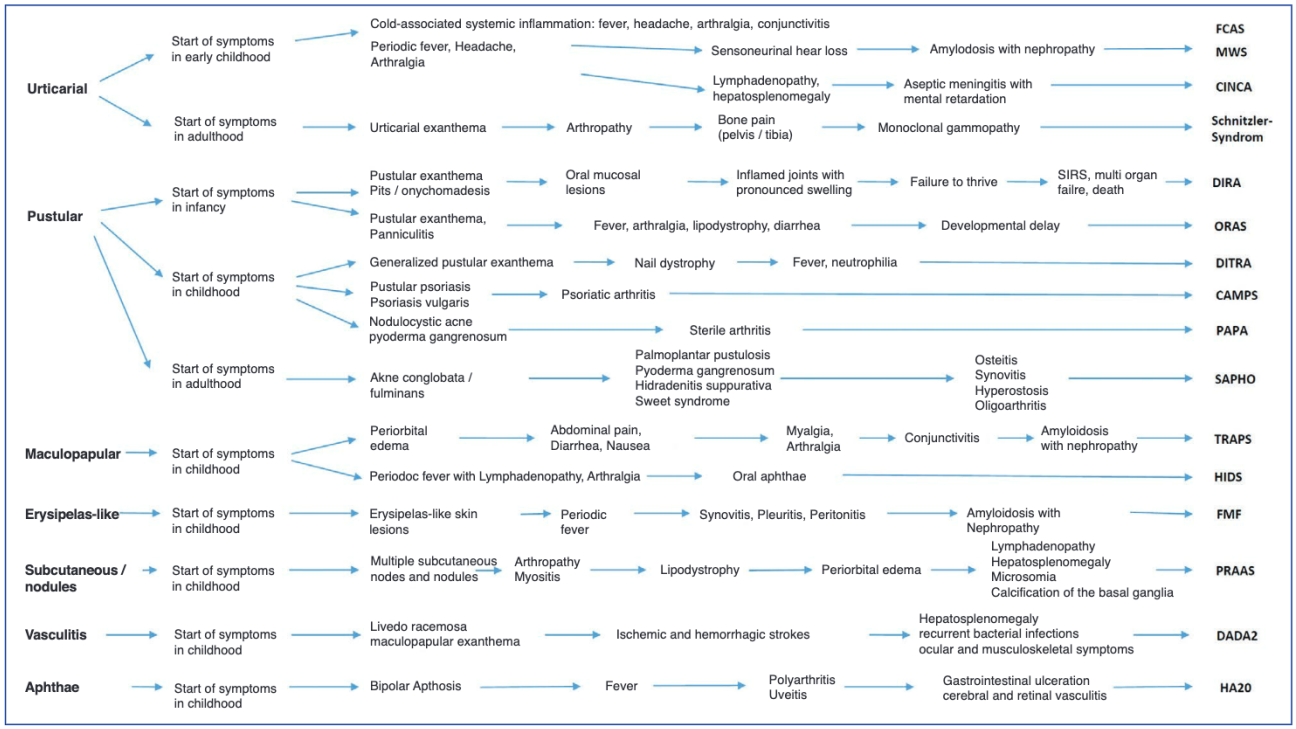

Figure 7 Classification of autoinflammatory syndromes according to efflorescences.
Abbr.: CAMPS, CARD14-mediated psoriasis; DADA2, adenosine deaminase 2 deficiency; DIRA, IL-1 receptor antagonist deficiency; DITRA, IL-36 receptor antagonist deficiency; FMF, familial Mediterranean fever; HA20, A20 haploinsufficiency; HIDS, hyper-IgD syndrome; ORAS, OTULIN-associated autoinflammatory syndrome; PAPA, pyogenic arthritis with pyoderma gangrenosum and acne; PRAAS, proteasome-associated autoinflammatory syndromes; SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis; SIRS: systemic inflammatory response syndrome; TRAPS, TNF-receptor-associated periodic syndrome.

skin is not sufficient, but an entire and comprehensive analysis of the patient's medical history is important. In the case of recurring systemic signs of inflammation such as fever and joint pain without a clear etiology, autoinflammatory syndromes should be considered. Therefore, a close collaboration with other specialization by medical specialty, such as rheumatology, is essential.

Conclusions

Autoinflammatory syndromes are a rare group of diseases that result from the dysfunction of the innate immune system. Many different pathomechanisms lead to an excessive response of the innate immune system (autoinflammation), which results in systemic inflammatory diseases. In recent years, a lot of progress has been made in research and development of diagnostics of autoinflammatory syndromes. Thanks to the latest sequencing technologies, a large number of mutations could be detected, diagnostics expanded and new targeted therapies developed.

Acknowledgements

We thank Prof. Kathrin Alexandra Uta Giehl (LMU Munich), Dr. Nicole Knöpfel (Children's Hospital Zurich), and Dr. Ifigenia Spanoudi-Kitrimi (ZU Leuven) for selecting and providing clinical images.

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd.

References

1 Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. Mol Cell 2002; 10: 417–26.

2 Sanchez GA, de Jesus AA, Goldbach-Mansky R. Monogenic autoinflammatory diseases: disorders of amplified danger sensing and cytokine dysregulation. Rheum Dis Clin North Am 2013; 39: 701–34.

3 Feldmann J, Prieur AM, Quartier P et al. Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes. Am J Hum Genet 2002; 71: 198–203.

4 Hoffman HM, Mueller JL, Broide DH et al. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. Nat Genet 2001; 29: 301–5.

5 Hoffman HM, Wanderer AA, Broide DH. Familial cold autoinflammatory syndrome: phenotype and genotype of an autosomal dominant periodic fever. J Allergy Clin Immunol 2001; 108: 615–20.

6 Muckle TJ. The "Muckle-Wells" syndrome. Br J Dermatol 1979; 100: 87–92.

7 Prieur AM, Griscelli C. Arthropathy with rash, chronic meningitis, eye lesions, and mental retardation. J Pediatr 1981; 99: 79–83.

8 Kieffer C, Cribier B, Lipsker D. Neutrophilic urticarial dermatosis: a variant of neutrophilic urticaria strongly associated with systemic disease. Report of 9 new cases and review of the literature. Medicine (Baltimore) 2009; 88: 23–31.

9 Johnstone RF, Dolen WK, Hoffman HM. A large kindred with familial cold autoinflammatory syndrome. Ann Allergy Asthma Immunol 2003; 90: 233–7.

10 Hashkes PJ, Toker O. Autoinflammatory syndromes. Pediatr Clin North Am 2012; 59: 447–70.

11 Federici S, Caorsi R, Gattorno M. The autoinflammatory diseases. Swiss Med Wkly 2012; 142: w13602.

12 Hill SC, Namde M, Dwyer A et al. Arthropathy of neonatal onset multisystem inflammatory disease (NOMID/CINCA). Pediatr Radiol 2007; 37: 145–52.

13 Kuemmerle-Deschner JB, Ozen S, Tyrrell PN et al. Diagnostic criteria for cryopyrin-associated periodic syndrome (CAPS). Ann Rheum Dis 2017; 76: 942–7.

14 Yu JR, Leslie KS. Cryopyrin-associated periodic syndrome: an update on diagnosis and treatment response. Curr Allergy Asthma Rep 2011; 11: 12–20.

15 Kone-Paut I, Galeotti C. Anakinra for cryopyrin-associated periodic syndrome. Expert Rev Clin Immunol 2014; 10: 7–18.

16 Hawkins PN, Lachmann HJ, McDermott MF. Interleukin-1-receptor antagonist in the Muckle-Wells syndrome. N Engl J Med 2003; 348: 2583–4.

17 Kuemmerle-Deschner JB, Haug I. Canakinumab in patients with cryopyrin-associated periodic syndrome: an update for clinicians. Ther Adv Musculoskelet Dis 2013; 5: 315–29.

18 Lachmann HJ, Lowe P, Felix SD et al. In vivo regulation of interleukin 1beta in patients with cryopyrin-associated periodic syndromes. J Exp Med 2009; 206: 1029–36.

19 Hoffman HM, Throne ML, Amar NJ et al. Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies. Arthritis Rheum 2008; 58: 2443–52.

20 Hoffman HM, Throne ML, Amar NJ et al. Long-term efficacy and safety profile of rilonacept in the treatment of cryopyrin-associated periodic syndromes: results of a 72-week open-label extension study. Clin Ther 2012; 34: 2091–103.

21 Garg M, de Jesus AA, Chapelle D et al. Rilonacept maintains long-term inflammatory remission in patients with deficiency of the IL-1 receptor antagonist. JCI Insight 2017; 2.

22 Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. The International FMF Consortium. Cell 1997; 90: 797–807.

23 French FMFC. A candidate gene for familial Mediterranean fever. Nat Genet 1997; 17: 25–31.

Correspondence to

Barbara Meier-Schiesser, MD, PhD
Department of Dermatology
University Hospital Zurich

Gloriastrasse 31
9091 Zurich, Switzerland

E-mail: barbara.meier-schiesser@usz.ch

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd. | JDDG | 1610-0379/2021/1903

24 Padeh S, Livneh A, Pras E et al. Familial Mediterranean fever in the first two years of life: a unique phenotype of disease in evolution. J Pediatr 2010; 156: 985–9.
25 Zimand S, Tauber T, Hegesch T, Aladjem M. Familial Mediterranean fever presenting with massive cardiac tamponade. Clin Exp Rheumatol 1994; 12: 67–9.
26 Kees S, Langevitz P, Zemer D et al. Attacks of pericarditis as a manifestation of familial Mediterranean fever (FMF). QJM 1997; 90: 643–7.
27 Lachmann HJ, Sengul B, Yavuzsen TU et al. Clinical and subclinical inflammation in patients with familial Mediterranean fever and in heterozygous carriers of MEFV mutations. Rheumatology (Oxford) 2006; 45: 746–50.
28 Zemer D, Revach M, Pras M et al. A controlled trial of colchicine in preventing attacks of familial mediterranean fever. N Engl J Med 1974; 291: 932–4.
29 Houten SM, Kuis W, Duran M et al. Mutations in MVK, encoding mevalonate kinase, cause hyperimmunoglobulinaemia D and periodic fever syndrome. Nat Genet 1999; 22: 175–7.
30 Drenth JP, Cuisset L, Grateau G et al. Mutations in the gene encoding mevalonate kinase cause hyper-IgD and periodic fever syndrome. International Hyper-IgD Study Group. Nat Genet 1999; 22: 178–81.
31 van derHilst JC, Bodar EJ, Barron KS et al. Long-term follow-up, clinical features, and quality of life in a series of 103 patients with hyperimmunoglobulinemia D syndrome. Medicine (Baltimore) 2008; 87: 301–10.
32 Drenth JP, Boom BW, Toonstra J, Van der Meer JW. Cutaneous manifestations and histologic findings in the hyperimmunoglobulinemia D syndrome. International Hyper IgD Study Group. Arch Dermatol 1994; 130: 59–65.
33 Hansmann S, Lainka E, Horneff G et al. Consensus protocols for the diagnosis and management of the hereditary autoinflammatory syndromes CAPS, TRAPS and MKD/HIDS: a German PRO-KIND initiative. Pediatr Rheumatol Online J 2020; 18: 17.
34 Kostjukovits S, Kalliokoski L, Antila K, Korppi M. Treatment of hyperimmunoglobulinemia D syndrome with biologics in children: review of the literature and Finnish experience. Eur J Pediatr 2015; 174: 707–14.
35 Aksentijevich I, Masters SL, Ferguson PJ et al. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. N Engl J Med 2009; 360: 2426–37.
36 Goldbach-Mansky R. Immunology in clinic review series; focus on autoinflammatory diseases: update on monogenic autoinflammatory diseases: the role of interleukin (IL)-1 and an emerging role for cytokines beyond IL-1. Clin Exp Immunol 2012; 167: 391–404.
37 Thacker PG, Binkovitz LA, Thomas KB. Deficiency of interleukin-1-receptor antagonist syndrome: a rare auto-inflammatory condition that mimics multiple classic radiographic findings. Pediatr Radiol 2012; 42: 495–8.
38 Reddy S, Jia S, Geoffrey R et al. An autoinflammatory disease due to homozygous deletion of the IL1RN locus. N Engl J Med 2009; 360: 2438–44.
39 Schnellbacher C, Ciocca G, Menendez R et al. Deficiency of interleukin-1 receptor antagonist responsive to anakinra. Pediatr Dermatol 2013; 30: 758–60.
40 Herlin T, Fiirgaard B, Bjerre M et al. Efficacy of anti-IL-1 treatment in Majeed syndrome. Ann Rheum Dis 2013; 72: 410–3.
41 Pinto-Fernandez C, Seoane-Reula ME. Efficacy of treatment with IL-1RA in Majeed syndrome. Allergol Immunopathol (Madr) 2017; 45: 99–101.
42 Vitale A, Rigante D, Lucherini OM et al. Biological treatments: new weapons in the management of monogenic autoinflammatory disorders. Mediators Inflamm 2013; 2013: 939847.
43 Wise CA, Gillum JD, Seidman CE et al. Mutations in CD2BP1 disrupt binding to PTP PEST and are responsible for PAPA syndrome, an autoinflammatory disorder. Hum Mol Genet 2002; 11: 961–9.
44 Smith EJ, Allantaz F, Bennett L et al. Clinical, molecular, and genetic characteristics of PAPA Syndrome: A review. Curr Genomics 2010; 11: 519–27.
45 Demidowich AP, Freeman AF, Kuhns DB et al. Brief report: genotype, phenotype, and clinical course in five patients with PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne). Arthritis Rheum 2012; 64: 2022–7.

 © 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd.

46 Cortis E, De Benedetti F, Insalaco A et al. Abnormal production of tumor necrosis factor (TNF)-alpha and clinical efficacy of the TNF inhibitor etanercept in a patient with PAPA syndrome [corrected]. J Pediatr 2004; 145: 851–5.
47 Stichweh DS, Punaro M, Pascual V. Dramatic improvement of pyoderma gangrenosum with infliximab in a patient with PAPA syndrome. Pediatr Dermatol 2005; 22: 262–5.
48 Dierselhuis MP, Frenkel J, Wulffraat NM, Boelens JJ. Anakinra for flares of pyogenic arthritis in PAPA syndrome. Rheumatology (Oxford) 2005; 44: 406–8.
49 Brenner M, Ruzicka T, Plewig G et al. Targeted treatment of pyoderma gangrenosum in PAPA (pyogenic arthritis, pyoderma gangrenosum and acne) syndrome with the recombinant human interleukin-1 receptor antagonist anakinra. Br J Dermatol 2009; 161: 1199–201.
50 Braun-Falco M, Kovnerystyy O, Lohse P, Ruzicka T. Pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH)–a new autoinflammatory syndrome distinct from PAPA syndrome. J Am Acad Dermatol 2012; 66: 409–15.
51 Ursani MA, Appleyard J, Whiteru O. Pyogenic arthritis, pyoderma gangrenosum, acne, suppurative hidradenitis (PA-PASH) syndrome: An atypical presentation of a rare syndrome. Am J Case Rep 2016; 17: 587–91.
52 Marzano AV, Ceccherini I, Gattorno M et al. Association of pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH) shares genetic and cytokine profiles with other autoinflammatory diseases. Medicine (Baltimore) 2014; 93: e187.
53 Salles M, Olive A, Perez-Andres R et al. The SAPHO syndrome: a clinical and imaging study. Clin Rheumatol 2011; 30: 245–9.
54 Colina M, Trotta F. Clinical and radiological characteristics of SAPHO syndrome. Curr Rheumatol Rev 2013; 9: 22–7.
55 Colina M, Pizzirani C, Khodeir M et al. Dysregulation of P2X7 receptor-inflammasome axis in SAPHO syndrome: successful treatment with anakinra. Rheumatology (Oxford) 2010; 49: 1416–8.
56 Wendling D, Prati C, Aubin F. Anakinra treatment of SAPHO syndrome: short-term results of an open study. Ann Rheum Dis 2012; 71: 1098–100.
57 Nguyen MT, Borchers A, Selmi C et al. The SAPHO syndrome. Semin Arthritis Rheum 2012; 42: 254–65.
58 Cianci F, Zoli A, Gremese E, Ferraccioli G. Clinical heterogeneity of SAPHO syndrome: challenging diagnose and treatment. Clin Rheumatol 2017; 36: 2151–8.
59 Kim CH, Kadhim S, Julien C. Treatment of pain in SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome. PM R 2014; 6: 92–5.
60 Hayem G, Bouchaud-Chabot A, Benali K et al. SAPHO syndrome: a long-term follow-up study of 120 cases. Semin Arthritis Rheum 1999; 29: 159–71.
61 Just A, Adams S, Brinkmeier T et al. Successful treatment of primary chronic osteomyelitis in SAPHO syndrome with bisphosphonates. J Dtsch Dermatol Ges 2008; 6: 657–60.
62 Ben Abdelghani K, Dran DG, Gottenberg JE et al. Tumor necrosis factor-alpha blockers in SAPHO syndrome. J Rheumatol 2010; 37: 1699–704.
63 deKoning HD. Schnitzler's syndrome: lessons from 281 cases. Clin Transl Allergy 2014; 4: 41.
64 Lipsker D. The Schnitzler syndrome. Orphanet J Rare Dis 2010; 5: 38.
65 Gouveia AI, Micaelo M, Pierdomenico F, Freitas JP. Schnitzler syndrome: a dramatic response to anakinra. Dermatol Ther (Heidelb) 2016; 6: 299–302.
66 Lipsker D, Veran Y, Grunenberger F et al. The Schnitzler syndrome. Four new cases and review of the literature. Medicine (Baltimore) 2001; 80: 37–44.
67 Bachelez H, Choon SE, Marrakchi S et al. Inhibition of the interleukin-36 pathway for the treatment of generalized pustular psoriasis. N Engl J Med 2019; 380: 981–3.
68 Hospach T, Glowatzki F, Blankenburg F et al. Scoping review of biological treatment of deficiency of interleukin-36 receptor antagonist (DITRA) in children and adolescents. Pediatr Rheumatol Online J 2019; 17: 37.
69 Boehner A, Navarini AA, Eyerich K. Generalized pustular psoriasis – a model disease for specific targeted immunotherapy, systematic review. Exp Dermatol 2018; 27: 1067–77.
70 Wouters CH, Maes A, Foley KP et al. Blau syndrome, the prototypic auto-inflammatory granulomatous disease. Pediatr Rheumatol Online J 2014; 12: 33.

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd. | JDDG | 1610-0379/2021/1903

71 Schaffer JV, Chandra P, Keegan BR et al. Widespread granulomatous dermatitis of infancy: an early sign of Blau syndrome. Arch Dermatol 2007; 143: 386–91.
72 Ikeda K, Kambe N, Satoh T et al. Preferentially inflamed tendon sheaths in the swollen but not tender joints in a 5-year-old boy with Blau syndrome. J Pediatr 2013; 163: 1525 e1.
73 Simonini G, Xu Z, Caputo R et al. Clinical and transcriptional response to the long-acting interleukin-1 blocker canakinumab in Blau syndrome-related uveitis. Arthritis Rheum 2013; 65: 513–8.
74 Chen J, Luo Y, Zhao M et al. Effective treatment of TNFα inhibitors in Chinese patients with Blau syndrome. Arthritis Res Ther 2019; 21: 236.
75 Millington GWM, Dobson J, Holden S et al. Sporadic Blau syndrome treated with adalimumab. Clin Exp Dermatol 2019; 44: 811–3.
76 Naik AU, Annamalai R, Biswas J. Uveitis in sporadic Blau syndrome: Long-term follow-up of a refractory case treated successfully with adalimumab. Indian J Ophthalmol 2018; 66: 1483–5.
77 Craiglow BG, Boyden LM, Hu R et al. CARD14-associated papulosquamous eruption: A spectrum including features of psoriasis and pityriasis rubra pilaris. J Am Acad Dermatol 2018; 79: 487–94.
78 Signa S, Campione E, Rusmini M et al. Whole exome sequencing approach to childhood onset familial erythrodermic psoriasis unravels a novel mutation of CARD14 requiring unusual high doses of ustekinumab. Pediatr Rheumatol Online J 2019; 17: 38.
79 Zhou Q, Yu X, Demirkaya E et al. Biallelic hypomorphic mutations in a linear deubiquitinase define otulipenia, an early-onset autoinflammatory disease. Proc Natl Acad Sci U S A 2016; 113: 10127–32.
80 Damgaard RB, Walker JA, Marco-Casanova P et al. The deubiquitinase OTULIN is an essential negative regulator of inflammation and autoimmunity. Cell 2016; 166: 1215–30 e20.
81 Zhou Q, Wang H, Schwartz DM et al. Loss-of-function mutations in TNFAIP3 leading to A20 haploinsufficiency cause an early-onset autoinflammatory disease. Nat Genet 2016; 48: 67–73.
82 Shigemura T, Kaneko N, Kobayashi N et al. Novel heterozygous C243Y A20/TNFAIP3 gene mutation is responsible for chronic inflammation in autosomal-dominant Behçet's disease. RMD Open 2016; 2: e000223.
83 Yu MP, Xu XS, Zhou Q et al. Haploinsufficiency of A20 (HA20): updates on the genetics, phenotype, pathogenesis and treatment. World J Pediatr 2020; 16(6): 575–84.
84 Ohnishi H, Kawamoto N, Seishima M et al. A Japanese family case with juvenile onset Behcet's disease caused by TNFAIP3 mutation. Allergol Int 2017; 66: 146–8.
85 Zhou Q, Wang H, Schwartz DM et al. Loss-of-function mutations in TNFAIP3 leading to A20 haploinsufficiency cause an early-onset autoinflammatory disease. Nat Genet 2016; 48: 67–73.
86 McDermott MF, Aksentijevich I, Galon J et al. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. Cell 1999; 97: 133–44.
87 Toro JR, Aksentijevich I, Hull K et al. Tumor necrosis factor receptor-associated periodic syndrome: a novel syndrome with cutaneous manifestations. Arch Dermatol 2000; 136: 1487–94.
88 Nakamura M, Kobayashi M, Tokura Y. A novel missense mutation in tumour necrosis factor receptor superfamily 1A (TNFRSF1A) gene found in tumour necrosis factor receptor-associated periodic syndrome (TRAPS) manifesting adult-onset Still disease-like skin eruptions: report of a case and review of the Japanese patients. Br J Dermatol 2009; 161: 968–70.
89 Nedjai B, Hitman GA, Quillinan N et al. Proinflammatory action of the antiinflammatory drug infliximab in tumor necrosis factor receptor-associated periodic syndrome. Arthritis Rheum 2009; 60: 619–25.
90 Gattorno M, Pelagatti MA, Meini A et al. Persistent efficacy of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome. Arthritis Rheum 2008; 58: 1516–20.
91 Gattorno M, Obici L, Cattalini M et al. Canakinumab treatment for patients with active recurrent or chronic TNF receptor-associated periodic syndrome (TRAPS): an open-label, phase II study. Ann Rheum Dis 2017; 76(1): 173–8.

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd.

92 Zhou Q, Yang D, Ombrello AK et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. N Engl J Med 2014; 370: 911–20.
93 Skrabl-Baumgartner A, Plecko B, Schmidt WM et al. Autoimmune phenotype with type I interferon signature in two brothers with ADA2 deficiency carrying a novel CECR1 mutation. Pediatr Rheumatol Online J 2017; 15: 67.
94 Rama M, Duflos C, Melki I et al. A decision tree for the genetic diagnosis of deficiency of adenosine deaminase 2 (DADA2): a French reference centres experience. Eur J Hum Genet 2018; 26: 960–71.
95 Springer JM, Gierer SA, Jiang H et al. Deficiency of adenosine deaminase 2 in adult siblings: many years of a misdiagnosed disease with severe consequences. Front Immunol 2018; 9: 1361.
96 Hashem H, Kumar AR, Muller I et al. Hematopoietic stem cell transplantation rescues the hematological, immunological, and vascular phenotype in DADA2. Blood 2017; 130: 2682–8.
97 Kanazawa N. Nakajo-Nishimura syndrome: an autoinflammatory disorder showing pernio-like rashes and progressive partial lipodystrophy. Allergol Int 2012; 61: 197–206.
98 Brehm A, Liu Y, Sheikh A et al. Additive loss-of-function proteasome subunit mutations in CANDLE/PRAAS patients promote type I IFN production. J Clin Invest 2015; 125: 4196–211.
99 Boyadzhiev M, Marinov L, Boyadzhiev V et al. Disease course and treatment effects of a JAK inhibitor in a patient with CANDLE syndrome. Pediatr Rheumatol Online J 2019; 17: 19.
100 Crow YJ, Casanova JL. STING-associated vasculopathy with onset in infancy–a new interferonopathy. N Engl J Med 2014; 371: 568–71.
101 Shwin KW, Lee CR, Goldbach-Mansky R. Dermatologic manifestations of monogenic autoinflammatory diseases. Dermatol Clin 2017; 35: 21–38.
102 Liu Y, Jesus AA, Marrero B et al. Activated STING in a vascular and pulmonary syndrome. N Engl J Med 2014; 371: 507–18.
103 Jain A, Misra DP, Sharma A et al. Vasculitis and vasculitis-like manifestations in monogenic autoinflammatory syndromes. Rheumatol Int 2018; 38: 13–24.
104 Sanchez GAM, Reinhardt A, Ramsey S et al. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. J Clin Invest 2018; 128: 3041–52.
105 Imhof L, Meier B, Frei P et al. Severe Sweet's syndrome with elevated cutaneous interleukin-1beta after azathioprine exposure: case report and review of the literature. Dermatology 2015; 230: 293–8.
106 Kolios AG, Maul JT, Meier B et al. Canakinumab in adults with steroid-refractory pyoderma gangrenosum. Br J Dermatol 2015; 173: 1216–23.
107 Navarini AA, Satoh TK, French LE. Neutrophilic dermatoses and autoinflammatory diseases with skin involvement–innate immune disorders. Semin Immunopathol 2016; 38: 45–56.
108 Satoh TK, Mellett M, Contassot E, French LE. Are neutrophilic dermatoses autoinflammatory disorders? Br J Dermatol 2018; 178: 603–13.
109 Meier B, Maul JT, French LE. Pyoderma gangrenosum and Sweet's syndrome: Cutaneous manifestations of autoinflammatory disorders. Hautarzt 2016; 67: 934–9.

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd.

[CME-Questions/ Lernerfolgskontrolle]

1. Zu den klassischen Fiebersyndromen zählt ...

a) Schnitzler-Syndrom
b) Pyoderma gangraenosum, Acne and Hidradenitis suppurativa (PASH)
c) Cryopyrin-assoziierte periodische Syndrome
d) TNFα-Rezeptor-assoziiertes periodisches Syndrom (TRAPS)
e) A20-Haploinsuffizienz (HA20)

2. Welche Aussage zur Therapie der autoinflammatorischen Syndrome ist richtig?

a) Systemische Steroide können unbegrenzt zur Therapie der autoinflammatorischen Syndrome eingesetzt werden.
b) Adalimumab ist Erstlinientherapie bei allen autoinflammatorischen Syndromen.
c) Canakinumab ist ein polyklonaler Antikörper gegen IL-1β.
d) Anakinra ist ein humaner Interleukin-1-Rezeptorantagonist.
e) Rilonacept wird seit vielen Jahren erfolgreich zur Behandlung der Autoinflammationssyndrome eingesetzt.

3. Welche der folgenden Syndrome ist nicht monogen?

a) PAPA-Syndrom
b) DADA2
c) SAPHO-Syndrom
d) Familiäres Mittelmeerfieber
e) DITRA

4. Welche Aussage zum TRAPS trifft nicht zu?

a) Die Patienten können unter abdominellen Schmerzen, Diarrhoe und Erbrechen leiden.
b) Ein charakteristisches Symptom ist ein periorbitales Ödem.
c) Die Patienten haben einen Gelenkbefall.
d) Das betroffene Gen bei TRAPS ist *TNFRSF1A*.
e) Die Patienten haben in der Regel keinen Hautbefall.

5. Bei welchem autoinflammatorischen Syndrom entwickelt sich typischerweise eine Psoriasis vulgaris oder pustulosa?

a) TRAPS
b) CAMPS
c) HA20
d) SAVI
e) Majeed-Syndrom

6. Welches Syndrom gehört zu den Interferon-mediierten Erkrankungen?

a) DIRA
b) SAPHO
c) CAMPS
d) HIDS
e) SAVI

7. Welche Kombination Syndrom – Gen trifft zu?

a) TRAPS – $TNFAIP_3$
b) FMF – MEFV
c) DIRA – IL36RN
d) SAVI – $CECR_1$
e) SAPHO – $NLRP_3$

8. Zu den CAPS-typischen Symptomen zählt nicht ...

a) Skelettdeformitäten
b) chronische aseptische Meningitis
c) sensoneurinaler Hörverlust
d) Vaskulitis
e) Urtikaria

9 Das Schnitzler-Syndrom ist in vielen Fällen assoziiert mit ...

a) erhöhten Bilirubinwerten
b) Eosinophilie
c) monoklonaler Gammopathie vom Typ IgM
d) Gefäßveränderungen
e) erhöhten Kreatininwerten

10. Das SAPHO-Syndrom äußert sich an der Haut häufig durch ...

a) Aphthen
b) Livedo reticularis
c) palmoplantare Pustulose
d) Ulzerationen
e) Erysipel

Liebe Leserinnen und Leser,
der Einsendeschluss an die DDA für diese Ausgabe ist der 31. Mai 2021.
Die richtige Lösung zum Thema Skleromyxödem in Heft 12 (Dezember 2020) ist:
(1c, 2d, 3a, 4b, 5b, 6d, 7c, 8b, 9a, 10e).

Bitte verwenden Sie für Ihre Einsendung das aktuelle Formblatt auf der folgenden Seite oder aber geben Sie Ihre Lösung online unter http://jddg.akademie-dda.de ein.

© 2021 Deutsche Dermatologische Gesellschaft (DDG). Published by John Wiley & Sons Ltd.