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A practical approach to the diagnosis of autoinflammatory diseases in childhood



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A B S T R A C T

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Autoinflammatory diseases are characterized by the presence of chronic or recurrent systemic inflammation secondary to abnormal activation of innate immunity pathways. Many of these diseases have been found to have mutations in the genes within these pathways. Due to their rarity, non-specific symptoms and the very recent genetic and phenotypic identification and recognition, a delay in diagnosis is common. Nevertheless, some specific clinical features should help the clinician to make the diagnosis. The purpose of this article is to provide a brief clinical description of these conditions and to present clinical flow-charts useful for a correct diagnosis of children with suspected autoinflammatory syndromes.

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Introduction

The autoinflammatory diseases are a group of rare diseases characterized by the presence of chronic or recurrent systemic inflammation, and defined by the over-activation of innate immunity mediators and cells (e.g. neutrophils, monocytes/macrophages). In contrast to the more common autoimmune diseases, cells of the adaptive immunity pathways (e.g. T and B lymphocytes) are only secondarily involved, as demonstrated by the persistent absence of autoantibodies and a lack of disease association with HLA class II genes [1,2].

In many cases of autoinflammatory diseases there is a family history of a similar illness. Mutations of genes that encode proteins essential in the recognition of foreign particles and the regulation of the inflammatory response have been found in the so-called monogenic or hereditary autoinflammatory

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diseases. New syndromes and genetic mutations continue to be added to the current list. In addition to the monogenic diseases, there is increasing evidence that the same mechanisms that initiate and maintain the inflammation in these rare disorders are also involved in a growing number of more common conditions, now identified as multifactorial autoinflammatory syndromes (see chapter by Ombrello et al. in this issue). In these conditions, there is overlap of dysfunction in both innate and adaptive immune systems (such as gout, systemic onset juvenile idiopathic arthritis, adult Still's disease, Crohn's disease, Behcet's disease, etc.) (Table 1) [1,2].

In this chapter we have proposed a rational and practical diagnostic approach to the most common monogenic and multifactorial autoinflammatory diseases with a paediatric onset, based on the most characteristic clinical presentation of these disorders.

Monogenic diseases

The child with periodic or recurrent fever

Fever is a very common symptom in children and, in most cases, is due to infections. Upper respiratory tract bacterial or viral infections (such as pharyngitis, tonsillitis and otitis media) and urinary tract infections are the most frequent causes of fever. In general, an infectious aetiology is the most common cause of recurrent fever in children under 6 years of age while autoimmune or inflammatory conditions (connective tissue diseases, inflammatory bowel diseases) are more common after the age of 6. Haematological malignancies may affect all age groups.

In these autoinflammatory diseases, the fever is recurrent, also described as periodic. Differential diagnoses of periodic fever in children are shown in Table 1.

The heritable autoinflammatory diseases occurring with periodic/recurrent fever are familial Mediterranean fever (FMF), tumor necrosis factor receptor associated periodic syndrome (TRAPS) and Mevalonate kinase deficiency (MKD) previously known as Hyper-IgD syndrome (HIDS) [3–7]. Many patients with very similar clinical features do not have the mutations described so far and so the hunt for new genes remains an active area of research. A clear example of this is PFAPA (Periodic Fever, Aphthous stomatitis, Pharyngitis Adenitis) syndrome, the most common periodic fever syndrome of childhood, that does not have a known genetic association [8,9].

How to recognize an autoinflammatory disease with periodic fever?

Fever. The child with a periodic fever syndrome has repeated, usually unprovoked, febrile episodes with temperature often above 39° in the absence of infection. The intervals between fever episodes can

Table 1

Main causes of periodic fever in childhood.

Infectious diseases	Recurrent upper respiratory tract infections Urinary tract infections Viral infections (EBV, Parvovirus B19, HSV1 and HSV2) Bacterial Infections (Borrelia, Brucella, salmonella, TBC) Parasitic diseases (Malaria, toxoplasmosis)
Congenital immune defects	Primary immunodeficiencies Cyclic neutropenia
Multifactorial Inflammatory diseases	Behcet's disease Systemic Lupus Erythematous (SLE) Crohn disease
Hereditary monogenic fevers	Familial Mediterranean fever Crypyrin associated periodic fevers (FCAS, MWS, CINCA/NOMID) TRAPS syndrome Mevalonate Kinase deficiency
Neoplastic diseases	Acute lymphoblastic leukemia Acute myeloid leukemia Lymphoma (Pel Epstein fever)
Idiopathic forms	PFAPA syndrome

be variable, except in the case of PFAPA that, most cases, display a regular pattern often recognized by parents that can predict when the next attack would be.

Other typical clinical features

- The child is usually very well between febrile episodes and grows normally. During attacks laboratory tests are characterized by leukocytosis and elevation of acute phase reactants that normalise completely in the periods between fever episodes [10]. This normalisation of symptoms and laboratory tests is characteristic and differentiates them from other diseases characterized by a chronic course (autoimmune diseases, neoplasm, inflammatory bowel diseases). In addition, these chronic diseases are associated with a progressive deterioration of the general condition of the patient and growth retardation. It is therefore essential to follow the patient presenting with recurrent fever episodes with complete wellbeing between the attacks for a sufficient period of time (at least 6–9 months) with the aid of a fever diary recorded by the parents documenting frequency, duration and associated symptoms and signs before a firm diagnosis of an autoinflammatory disease is made and before starting medications that might mask the diagnosis.
- The vast majority of patients display a disease onset in the first decade of life. However a variable percentage of patients with TRAPS syndrome and FMF may occasionally present a later disease onset, even in the second and third decade of life [10,11].
- A positive family history for recurrent or periodic fever may be of great relevance, especially for TRAPS (autosomal dominant inheritance), but also for FMF and MKD (autosomal recessive inheritance) [12]. It is important to note that, at the time of the suspicion in the proband the affected parent may present a more attenuated or less typical picture of the disease [12].

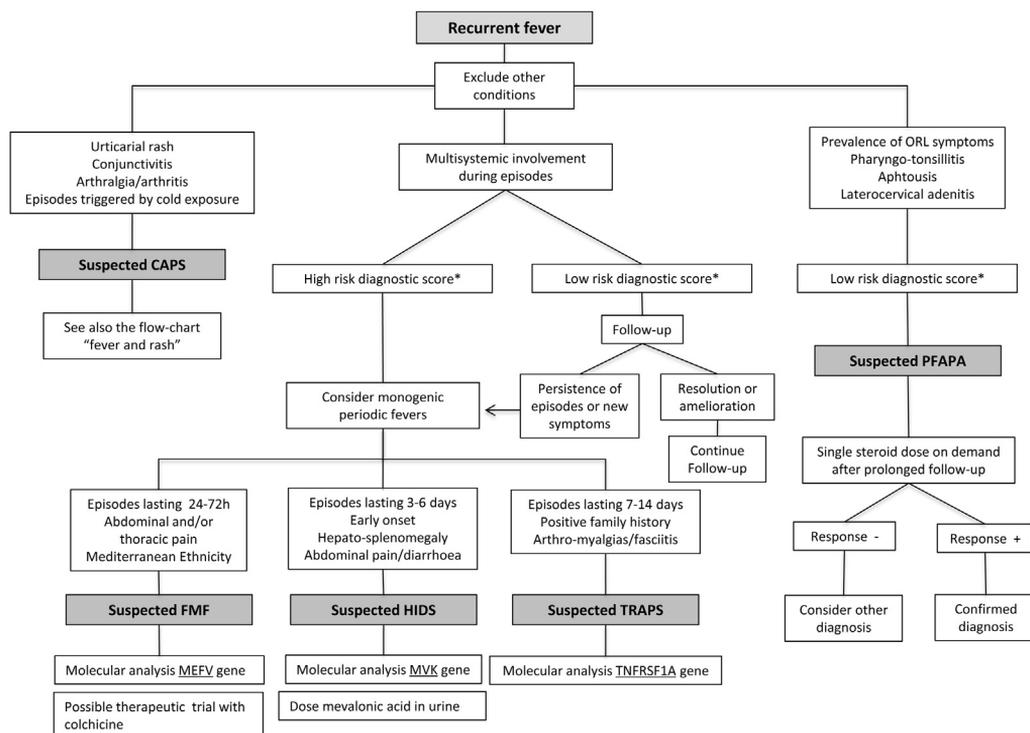


Fig. 1. Diagnostic flow-chart for a child with periodic/recurrent fever. “High risk diagnostic score” and “Low risk diagnostic score” mean respectively a score higher or lower of 15%, that represent the cut-off value with the best sensitivity and specificity (Gattorno et al. A&R 2008).

- Family history of complications of untreated autoinflammatory disease should also alert the physician, e.g. renal failure might be caused by amyloidosis [13].
- The ethnic origin of the patient and family is another relevant piece of information. This is of particular relevance for FMF, which has a high incidence in populations living in the Eastern Mediterranean basin and Middle East (Turks, Arabs, Armenians non-Ashkenazi Jewish) [14], but can be also observed in other South-European countries like Italy, Spain and Greece [15].

The duration of fever attacks and the clinical manifestations associated with fever episodes represent the “red flags” which should prompt the request for the molecular analysis of gene known to be associated with periodic fever, as shown in the algorithm in Fig 1.

- A very short duration (24–48 h) of fever and the presence of severe abdominal and/or chest pain indicate a possible diagnosis of Familial Mediterranean fever (*MEFV* gene mutations). Sometimes a very painful arthritis may be present but, in contrast with other rheumatologic conditions, it has a short-course and resolves with the termination of fever episode [16]. Cutaneous findings are less common than serosal or synovial involvement and most commonly are represented by an erysipeloid erythematous rash on the dorsum of the foot, ankle, or lower leg.
- Longer-lasting fever episodes (4–7 days) associated with extreme prostration, diffuse lymphadenopathy and splenomegaly, oral ulcers, skin rashes including palms and soles, abdominal pain and other gastrointestinal manifestations, such as vomiting or diarrhoea, should raise the suspicion of a possible MKD or HIDS (*MVK* gene mutations) [17]. The determination of urinary mevalonic acid at the time of fever episode is a useful screening test but unfortunately is performed only in specialized centres. High serum IgD and IgA are often seen, but these are not specific to this disease.
- TRAPS patients (*TNFRSF1A* gene mutations) generally present prolonged febrile episodes (over 7 days, up to 3 weeks). The associated symptoms may overlap with those already described for the other periodic fevers including different types of rash (erythema marginatum, urticarial or maculopapular rash). A maculo-papular, erythematous or urticarial rash are often associated with febrile

Diagnostic score

Age at onset (months): <input style="width: 50px;" type="text" value="18"/>
Abdominal pain: <input checked="" type="radio"/> Never <input type="radio"/> Sometimes <input type="radio"/> Often <input type="radio"/> Always
Aphthosis: <input type="radio"/> Never <input checked="" type="radio"/> Sometimes <input type="radio"/> Often <input type="radio"/> Always
Thoracic pain: <input type="radio"/> Never <input type="radio"/> Sometimes <input checked="" type="radio"/> Often <input type="radio"/> Always
Diarrhea: <input type="radio"/> Never <input checked="" type="radio"/> Sometimes <input type="radio"/> Often <input type="radio"/> Always
Family history: <input checked="" type="radio"/> Yes <input type="radio"/> No
<input type="button" value="Calculate"/>

The Diagnostic Score for Periodic Fever

PERIODIC AUTOINFLAMMATORY SYNDROMES

Score: 1,652

Probability to be positive (%): 19,9

Predicted GROUP: High risk

Fig. 2. Variables considered by the Gaslini diagnostic score for the determination of the risk to carry a causative mutation of genes associated to inherited periodic fevers (www.printo.it/periodicfevers).

episodes of MKD and TRAPS syndromes. In the latter the painful erythema related to the previously described fasciitis is definitely a distinctive element. The rash of MKD tends to be widespread and involve the palms and soles. FMF may be associated with a transient skin rash, erysipilas-like-erythema, often localized to the lower limbs (Fig. 3) [10].

- However, periorbital oedema with or without conjunctivitis and eye pain and severely painful fasciitis accompanied by erythema of the overlying skin, represent two rather distinctive manifestations of this condition (Fig. 1) [7,12,18].

In contrast with the inherited periodic fevers described above, fever episodes in PFAPA syndrome are generally dominated by fever in the absence of upper respiratory tract infection associated with at least one among the three characteristic symptoms of the acronym (pharyngitis, latero-cervical lymph adenopathy and aphthous stomatitis). In this case, the other organ manifestations (gastro-intestinal symptoms, rash, chest pain, muscle-skeletal manifestations) frequently observed in the monogenic diseases, whenever present, are usually quite mild and sporadic (Fig. 1) [19].

Tool for diagnosis

With the purpose of facilitating the physician in identifying which patients with periodic fever need genetic analysis, a diagnostic score was developed some years ago [20]. The score is able to calculate, on the basis of a simple algorithm, the probability (high vs low risk) for a child with periodic fever to carry clearly pathogenic mutations of genes responsible for three forms of monogenic periodic fever (MEFV, TNFRSF1A, MVK). This score is available on the web (www.printo.it/periodicfever) and is based on the presence/absence and frequency of 6 independent variables: age at onset, positive family history, presence of abdominal pain, chest pain, aphthous stomatitis and diarrhoea (Fig. 2) [20]. In the presence of a low score, usually observed in PFAPA patients, the probability to be carrier of one mutation is extremely low. In this case the patient should not be screened for genetic analysis [21]. The latter test

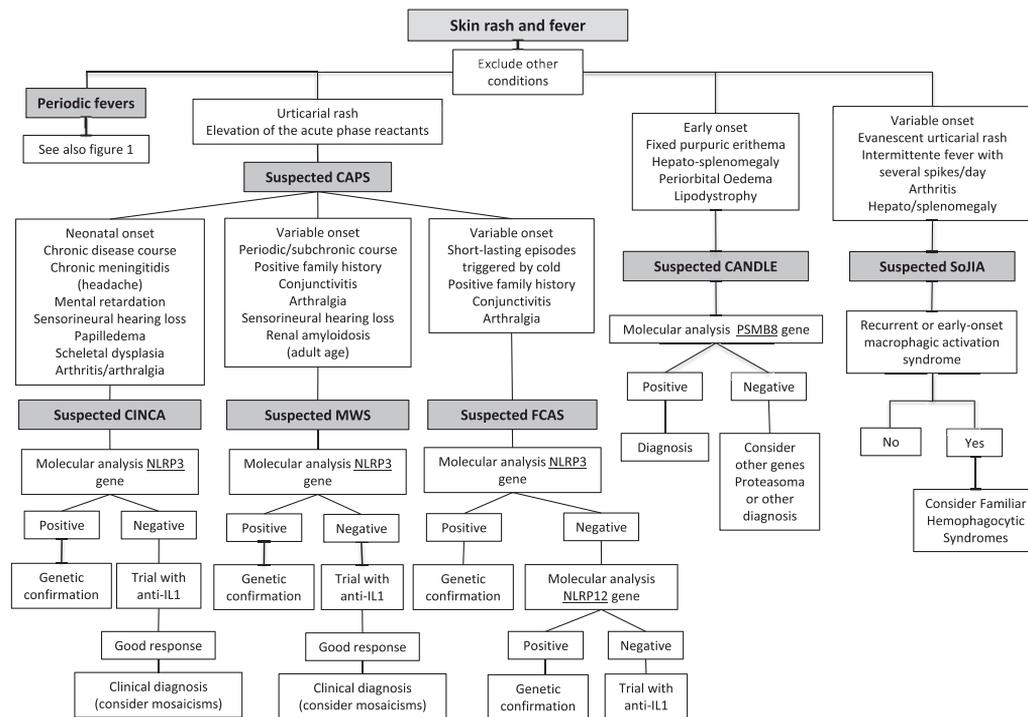


Fig. 3. Diagnostic flow-chart for a child with fever and skin rash.

might be performed later in case of persistence of the episodes and appearance of new clinical manifestations (Fig. 1) [20].

The child with chronic fever and rash

The association of fever and rash is a rather common occurrence in many infectious, haemato-oncologic and inflammatory diseases (Table 2).

Each of these categories has distinctive clinical features and their detailed description is beyond the scope of our article. However, it is useful to highlight that a skin rash is usually a salient feature of the monogenic or multifactorial autoinflammatory diseases.

The cryopyrin associated periodic syndromes (CAPS) are classically associated with a typical skin rash that represent the hallmark of these conditions [22,23] (Fig. 3). CAPS are a group of three diseases described in the last decades, associated with mutations of different parts of the same gene, the *NLRP3*, which encodes a protein named cryopyrin [22]. This protein acts as an intracellular recognition molecule for pathogens and other noxious stimuli. Mutations of *NLRP3* lead to a gain-of-function of the protein that is associated to an abnormal over-secretion of IL-1 β after cell stimulation. The clinical common denominator of these conditions is the presence of a chronic or recurrent systemic inflammation associated with a characteristic urticarial rash (Fig. 4). Familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS) and chronic infantile neurological cutaneous and articular (CINCA)(Neonatal onset multisystem inflammatory disease, NOMID) syndrome are the three conditions representing the clinical spectrum, from the mildest to the more severe, associated with different mutations in the *NLRP3* gene [23,24]. Mutations of *NLRP12* gene are associated to a rare syndrome affecting few families, known as type 2 FCAS [25].

It is also important to note that a skin rash (urticarial, erythematous, papular) might also characterize some fever episodes of the monogenic periodic fevers (TRAPS, MKD and FMF), already mentioned in the previous paragraph [10].

Table 2

Main causes of fever and rash in children.

Infectious diseases	
Bacterial	β hemolytic Streptococcal infections Borrelia Burgdoferi Rickettsia Mycoplasma Bartonella Henselae Salmonella Treponema Pallidum (congenital syphilis)
Parasitic	Toxoplasma
Viral	Exanthematous childhood diseases (rubella, varicella) Parvovirus B19 Adenovirus Cytomegalovirus Enteroviruses Epstein Barr virus HAV, HBV, HIV
Inflammatory diseases	
Multifactorial rheumatic diseases	Systemic Lupus Erythematous Systemic onset juvenile idiopathic arthritis Kawasaki disease, polyarteritis nodosa and other vasculitis Sarcoidosis
Monogenic autoinflammatory syndromes	Monogenic periodic fever (FMF,MKD, TRAPS) Cryopyrin associated periodic syndromes (FCAS, MWS, CINCA/NOMID) CANDLE syndrome
Hemato-oncologic diseases	
Tumors	Acute lymphoblastic leukemia, neuroblastoma Lymphomas
Congenital forms	Hereditary hemophagocytic syndromes



Fig. 4. Urticarial rash in a 16-year-old girls with Muckle–Wells syndrome.

A skin rash is also the manifestation of another new clinical entity, known as CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) syndrome (or Nakaio–Nishimura syndrome in the Japanese literature) [26,27]. This disease is characterized by an early onset panniculitis associated with fever and systemic inflammation. The skin manifestations progress to severe lipodystrophy. This condition is associated to mutations of the *PSMB8* gene encoding a protein belonging to the intracellular multi-protein complex called proteasome [28,29].

How to recognize an auto-inflammatory disease presenting with fever and rash?

The distinctive feature of CAPS is an urticarial rash associated with systemic inflammation and low-grade fever (Fig. 4).

As opposed to typical urticaria, though, the rash is usually not itchy and not associated with angioedema. It does not respond to anti-histamines drug. It lasts for a few hours and its distribution tends to change throughout the day without leaving purpuric or ecchymotic lesions.

In FCAS patients the rash appears along with signs of systemic inflammation (fever, asthenia, conjunctivitis, arthralgia and elevated inflammatory markers) after systemic exposure to cold. These patients must not be confused with those affected by contact cold urticaria (the ice cube test is always negative) or cold urticarial due to systemic cold exposure that are characterized by angioedema, absence of systemic inflammation and rapid response to anti-histamine treatment [30].

In Muckle–Wells syndrome, a sub-chronic or chronic course is usually observed. In this case the clinical manifestations are not associated to cold exposure. The urticarial rash is persistently associated with the elevation of acute phase reactants and with the clinical manifestations already described for FCAS [31]; in these patients articular involvement is usually more prominent in comparison to FCAS patients with the development of a frank arthritis. A biopsy of the skin lesions shows neutrophilic perivascular infiltration, with no signs of either vasculitis or epidermal oedema, typical of the histamine-mediated chronic urticaria [32]. Sensorineural hearing loss and renal amyloidosis are late onset complications in untreated patients [24]. The presence of similar clinical manifestations in other family members is, of course, strongly associated with the autosomal dominant pattern of inheritance of the disease. The absence of autoantibodies and the normal complement levels exclude hypocomplementemic urticarial vasculitis or other autoimmune diseases (SLE, other vasculitis).

In NOMID/CINCA syndrome, the most severe form of CAPS, all of the above mentioned clinical manifestations are characterized by a very early onset, usually at birth or during the first few days of life. Specific manifestations of this severe form are chronic aseptic meningitis (with development of headache, papilledema, and cerebral atrophy resulting in developmental delay), dysmorphic facial (prominent frontal bossing, hypoplasia of the face, saddle nose) and skeletal (metaphyseal dysplasia,

clubbing of the extremities) features [24,33]. These clinical manifestations are extremely indicative for CINCA syndrome and should be promptly recognized since early treatment with IL-1 blockade can prevent the development of severe neurologic complications [34]. This is an example of where identification of a genetic defect leads to a rational and very effective treatment for a very debilitating disease.

In cases of suspected CAPS the child must be evaluated in a specialized centre to perform the genetic analysis of the *NLRP3* gene. It is important to note that up to 40% of patients with a typical CAPS phenotype are negative for germline mutations in the *NLRP3* gene. Many of these individuals are carriers of somatic mosaicisms that can be detected in very specialized laboratories only [35,36].

In some rare families symptoms similar to those described in FCAS patients may be associated with mutations in the *NLRP12* gene [25,37]. This form is known as familial cold auto-inflammatory type 2 (FCAS2) syndrome.

CANDLE syndrome, a recently described disease caused by mutations in the *PSMB8* gene, enters into the differential diagnosis with CINCA for its early onset and severe systemic involvement. Beginning in the first weeks of life, the patients present with fever and systemic inflammation associated with the appearance of erythematous and purple lesions that tend to persist for a few weeks (and therefore much more stable over time than the urticarial rash described in CAPS patients) with residual purpuric lesions. The clinical and histological appearance of the lesions is consistent with a panniculitis. The most typical manifestation is represented by the progressive loss of subcutaneous fat, which leads in time to an evident lipodystrophy, that represents the most distinctive clinical feature of the disease [26].

During childhood, patients may present an erythematous periorbital edema and an enthesitis-arthritis of the small joints of the hands and feet. Hepatosplenomegaly is often present along with growth retardation [28].

The child with atypical form of chronic or recurrent arthritis

A number of different conditions (infectious, inflammatory, metabolic and hemato-oncologic), may be the cause of recurrent arthritis but the autoinflammatory diseases in which arthritis represents the predominant feature are the PAPA (pyogenic arthritis, pyoderma gangrenosum and acne) syndrome and Blau syndrome (see chapter on granulomatous diseases in this issue).

(Table 3) PAPA syndrome is historically characterized by the triad of pyogenic sterile arthritis, pyoderma gangrenosum and severe acne and is associated with mutations in the *PSTPIP1* gene [40]. Blau syndrome is associated with mutations of the *NOD2/CARD15* gene and is characterized by the triad of early onset poly-articular arthritis, skin rash and panuveitis [41] (Fig. 5). Both diseases have an autosomal dominant pattern of inheritance, although *de novo* mutations may be frequent.

When to suspect an autoinflammatory disease in a child with atypical arthritis?

The more characteristic feature of arthritis, in patients with PAPA syndrome, is its frank pyogenic appearance. The joint is extremely painful and swollen. Moreover, the arthrocentesis shows a purulent synovial fluid orientating towards a diagnosis of an infectious arthritis (Fig. 5).

Patients display a consensual increase of acute phase reactants with a neutrophilic leukocytosis, although fever rarely occurs [42].

The microbiological analysis of synovial fluid is persistently negative, and antibiotic treatment is ineffective. Conversely, a significant improvement of the severe clinical picture occurs with the use of non-steroidal anti-inflammatory drugs or, after the careful exclusion of an infection, with the use of intra-articular steroids. Indeed the recurrent of pyogenic and sterile arthritis, frequently observed after a non-penetrating trauma, is the more common manifestation of PAPA syndrome at its onset, especially in childhood [42]. The above-mentioned characteristics differentiate PAPA Syndrome from the other more common forms of inflammatory arthritis of childhood.

The typical cutaneous manifestations of the disease usually appear sometime after the joint involvement, often in the second decade of life. They are often extremely severe and annoying and sometimes disfiguring manifestations, such as pyoderma gangrenosum (Fig. 6), severe acne, skin abscesses, sterile furunculosis and suppurative hydroadenitis [40] (see Table 4). Often in the family other subjects suffering from one or more of these symptoms might be found (Fig. 5).

Table 3
Differential diagnosis in children with chronic or recurrent arthritis.

Monoarticular arthritis	Monoarticular JIA Septic arthritis Reactive arthritis Tuberculous arthritis Hemophilia Foreign body Vascular malformations Post-traumatic arthritis Neoplastic diseases (LLA, neuroblastoma)
Oligo/polyarticular arthritis	Villo-nodular synovitis Oligo/polyarticular JIA Arthritis in Lyme disease Reactive arthritis Inflammatory bowel diseases Metabolic diseases Connective tissue diseases (SLE, dermatomyositis) PAPA syndrome Blau syndrome/early onset sarcoid arthritis Monogenic periodic fevers (FMF, TRAPS, MKD)

In patients affected with Blau syndrome, the differential diagnosis with other inflammatory chronic recurrent form of arthritis is often more complex. In this case, patients usually develop very early in life (in the first 2–3 years) a difficult to treat polyarticular arthritis. The occurrence of uveitis (which often involves both the anterior and posterior chamber of the eye) might suggest the diagnosis of juvenile idiopathic arthritis. However, Antinuclear antibodies and rheumatoid factor are usually absent. Indeed, an experienced ophthalmologist would provide the correct diagnosis highlighting the presence of a granulomatous panuveitis [43,44]. The possible concomitant presence of a skin rash should suggest the appropriate diagnosis. Skin manifestations are quite variable ranging from a maculo-papular rash to polymorphic erythematous patches. Most typical and characteristic is a widespread rash often defined

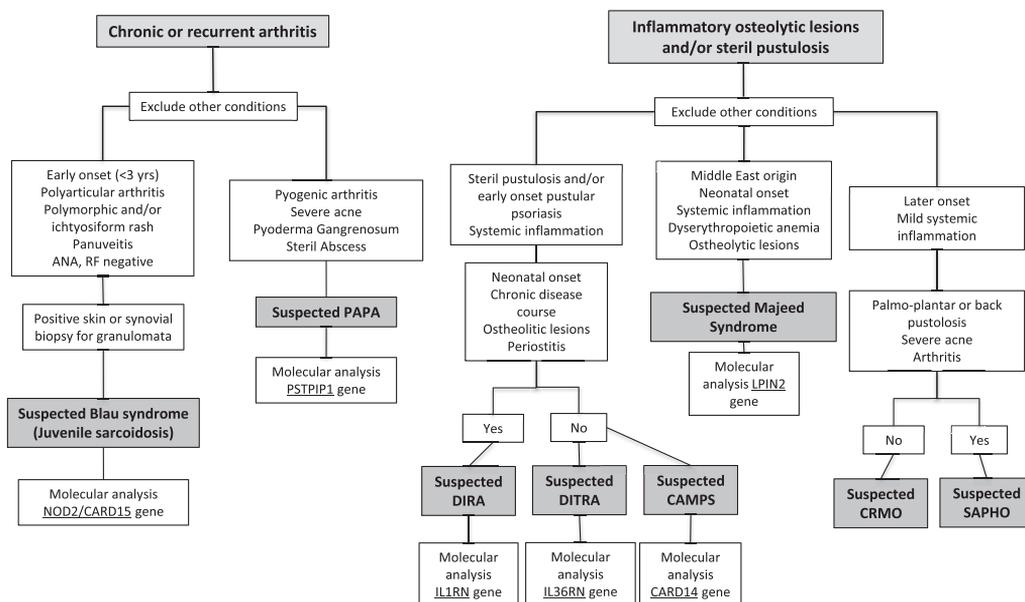


Fig. 5. Diagnostic flow-chart for a child with chronic recurrent arthritis and for a child with osteolytic lesions and/or sterile pustulosis.



Fig. 6. Pyoderma gangrenosum in a patients with PAPA syndrome.

as “ichthyosiform”, characterized by small reddish papules (Fig. 7). The careful observation of the joint involvement might also help to identify the peculiar predominance of a tenosynovitis, which gives to the joints a characteristic “boggy” appearance. A skin or synovial biopsy revealing the presence of typical granulomas must immediately orientate towards the diagnosis, which can be confirmed by molecular analysis of the *NOD2/CARD15* gene (Fig. 5) [45].

The child with pustular skin lesions and systemic inflammation

The early appearance of pustular skin lesions represents the possible presentation of some recently described monogenic auto-inflammatory diseases (Table 5). The DIRA syndrome (deficiency of IL-1 receptor antagonist) is linked to non-sense mutations in the *IL1RN* gene, which encodes the IL-1 receptor antagonist. The absence of this important mechanism for the inflammatory homeostasis leads to a very severe systemic inflammatory condition since birth accompanied by sterile pustulosis. Patients are extremely irritable. An X-ray may show the presence of inflammatory sterile osteolytic bone lesions associated with periostitis [46]. Due to the neonatal onset and the persistence of chronic inflammation, a primary immunodeficiency is usually suspected. However the absence of isolation of any pathogen from blood and skin lesions and the substantial lack of response to antibiotic therapy, should suggest this rare and severe inflammatory condition (Fig. 5), that should be promptly treated with the recombinant IL-1 receptor antagonist (anakinra) [46].

The absence of IL-36 receptor antagonist is instead responsible for the DITRA syndrome (deficiency of IL-36 receptor antagonist, *IL36RN* gene) which displays clear similarities with the pathogenesis and the clinical manifestations of DIRA syndrome but without bony lesions [47]. These patients present

Table 4

Main features of PAPA and Blau syndromes.

	Gene	Pattern of inheritance	Laboratory	Characteristic features of arthritis	Other clinical features
PAPA syndrome	<i>PSTPIP1</i>	Autosomal dominant	<ul style="list-style-type: none"> - ANA, RF usually negative - Neutrophilic leukocytosis - Increased CRP and ESR - Purulent synovial fluid 	<ul style="list-style-type: none"> - Oligoarticular - Extremely painful and swollen joints - Pyogenic aspect of synovial fluid with negative microbiological analysis. 	<ul style="list-style-type: none"> - Rarely fever - Cutaneous manifestations: <ul style="list-style-type: none"> - Pyoderma Gangrenosum - Severe acne - Skin abscesses - Sterile furunculosis - Suppurative hydroadenitis
BLAU syndrome	<i>NOD2/CARD15</i>	Autosomal dominant	<ul style="list-style-type: none"> - ANA, RF usually negative - Normal/increased acute phase reactants - Inflammatory synovial fluid 	<ul style="list-style-type: none"> - Polyarticular - Predominant tenosynovitis (“boggy” appearance) - Difficult to treat 	<ul style="list-style-type: none"> - Early onset - Granulomatous panuveitis - Skin rash



Fig. 7. Ichthyosiform rash and “boggy” arthritis of ankles in a patients with Blau's syndrome.

with pustular psoriasis. In conjunction with skin flares, patients display a clear systemic inflammation with fever and elevation of acute phase reactants. It should be noted that the pustular psoriasis has also been recently associated with another genetic defect being associated to mutations in the *CARD14* gene in an autosomal dominant disorder called CAMPS (CARD14-mediated pustular psoriasis) [48] (Fig. 5).

Multifactorial inflammatory diseases

Systemic juvenile idiopathic arthritis (SJIA)

The triad of intermittent fever with several spikes for day, rash and arthritis characterizes the most frequent multifactorial autoinflammatory disease observed in childhood: systemic juvenile idiopathic arthritis (SJIA). The skin rash has an urticarial-like appearance, often with salmon shades, and is typically associated with fever spikes, with rapid disappearance as the patient become afebrile [38]. Usually the systemic features (fever and rash) are prevalent at disease onset. The joint involvement can appear in the following weeks with a variable severity. Hepato-splenomegaly, generalized lymphadenopathy and polyserositis may be part of the clinical picture, as well as the development of a potentially lethal haematological complication named “macrophage activation syndrome” This event is characterized by a progressive deterioration of general condition associated with increased transaminases, LDH, triglycerides and cholesterol, hyperferritinemia and consumptive coagulopathy (see also the MAS article in this issue) [38]. The presence of this serious complication at the onset of the disease, especially in early childhood, must also raise the suspicion of a possible Familial Hemophagocytic syndrome (Fig. 3) [39].

The child with sterile inflammatory osteolytic lesions

Together with skin and joints, the bone can represent the typical site of inflammation in an interesting group of monogenic or multifactorial autoinflammatory diseases.

Also in this case the differential diagnosis of isolated or multiple osteolytic lesions is particularly broad and challenging (Table 6).

Table 5

Main features of autoinflammatory diseases presenting with aseptic pustulosis and/or pustular psoriasis.

	GENE	Pattern of inheritance	Main clinical features
DIRA	<i>IL1RN</i>	Autosomal recessive	<ul style="list-style-type: none"> - Neonatal onset - Severe chronic systemic inflammation - Aseptic pustulosis - Multifocal osteomyelitis - Periostitis
DITRA	<i>IL36RN</i>	Autosomal recessive	<ul style="list-style-type: none"> - Recurrent flares of pustular psoriasis with systemic inflammation - No involvement of other internal organs
CAMPS	<i>CARD14</i>	Autosomal dominant	<ul style="list-style-type: none"> - Recurrent flares of pustular psoriasis with systemic inflammation

In children and young people, the most common autoinflammatory condition affecting bones is represented by chronic recurrent multifocal osteomyelitis (CRMO), which currently is not associated with any known genetic mutation and is therefore considered a multifactorial form. CRMO usually appears during childhood, after the age of 8, with pain in one or more bones. The child is generally well otherwise, although the intensity of the pain can variably affect the quality of life and movement. The markers of inflammation are usually normal or slightly elevated. The diagnostic work-up is usually challenging and is based on the careful exclusion of infectious (Tuberculosis) or hemato-oncologic forms (sarcomas, bone lymphomas, neuroblastoma, histiocytosis) and hypophosphatasia [49] (Table 6). It is interesting that there is often a personal or family history of psoriasis or Crohn disease, both of which have disordered innate immunity as part of their pathogenesis.

In adolescents and young adults the bone involvement may be associated with severe acne, pustular lesions at the trunk and the extremity of the limbs together with an axial and/or peripheral arthritis. This association configures the diagnosis of SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis).

It is interesting to note that sterile osteolytic lesions represent also the main hallmark of a very rare monogenic autoinflammatory disease such as the above mentioned DIRA syndrome and Majeed's syndrome. This latter rare condition is associated to mutations of *LPIN2* gene and has been described only in populations of the Middle East [50]. In this systemic inflammatory disease osteolytic lesions similar to CRMO are associated with a typical picture of dyserythropoietic anemia and with skin lesions consistent with a neutrophilic dermatitis (Fig. 5). IL-1 blockade was recently shown to be dramatically effective in two brothers with Majeed syndrome [51].

Conclusions

As discussed, with respect to the original description of the first monogenic periodic fevers, the pattern of presentation of autoinflammatory syndromes has been greatly expanded with the identification of new diseases and gene mutations. The severe inflammatory involvement of the skin and of the osteo-articular system are rather common feature of many of these conditions, with a clinical overlaps among different diseases. However, the knowledge of the different combinations of clinical manifestations associated with these diseases, together with the careful exclusion of other conditions that enter into the differential diagnosis, should lead to suspicion a diagnosis of autoinflammatory disease and towards proceeding with molecular genetic analysis, which usually represent the final step for the definitive diagnosis.

It is important to point out, that the interpretation of genetic test is not free from pitfalls and misinterpretations and requires a thorough knowledge of the possible impact of genetic variants and their significance (high or low penetrance mutations, polymorphisms, etc). Moreover, “typical clinical pictures” may not yield a positive genetic test due to the incomplete stage in our knowledge of the genetic basis of these diseases. In this regard, cooperation between geneticists and specialized centres

Table 6
Differential diagnosis in children with osteolytic lesions.

Single osteolytic lesion	Idiopathic osteolysis Intraosseous lipoma Bone cyst Osteoid osteoma Subchondral cyst Ewing sarcoma Osteogenic sarcoma Hypophosphatasia
Multiple osteolytic lesions	Metastatic neoplasia (neuroblastoma, leukemia.) Bone Lymphoma Multiple myeloma Langerhans cell histiocytosis Hypophosphatasia Rosai–Dorfman disease

is usually pivotal for the correct characterization of patients with suspected autoinflammatory disease. The presence of genetic variation/mutation will then point to a rational method of treatment.

Learning points

- ✓ The autoinflammatory diseases are a group of rare diseases characterized by the presence of chronic or recurrent systemic inflammation and defined by the over-activation of innate immunity mediators and cells.
- ✓ Even if most of these diseases display a certain degree of clinical overlap, the presence of some distinctive features (“red flags”) may suggest the diagnosis.
- ✓ The presence of causative mutations in the genes responsible for monogenic autoinflammatory diseases confirm the clinical suspicions, but their absence does not exclude the clinical diagnosis as genetic variations are still being found.
- ✓ A part from FMF, no validated diagnostic criteria are available. An evidence-based diagnostic score represent a useful tool for the identification of patients at higher risk to carry a causative mutation in one of the genes associated to periodic fevers.

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