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PICTORIAL ESSAY

Autoinflammatory diseases in childhood, part 1: monogenic syndromes

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Abstract

Autoinflammatory diseases constitute a family of disorders defined by aberrant stimulation of inflammatory pathways without involving antigen-directed autoimmunity. They may be divided into monogenic and polygenic types. Monogenic autoinflammatory syndromes are those with identified genetic mutations, such as familial Mediterranean fever, tumor necrosis factor receptor-associated periodic fever syndrome (TRAPS), mevalonate kinase deficiency or hyperimmunoglobulin D syndrome, cryopyrin-associated periodic fever syndromes (CAPS), pyogenic arthritis pyoderma gangrenosum and acne (PAPA) syndrome, interleukin-10 and interleukin-10 receptor deficiencies, adenosine deaminase 2 deficiency and pediatric sarcoidosis. Those without an identified genetic mutation are known as polygenic and include systemic-onset juvenile idiopathic arthritis, idiopathic recurrent acute pericarditis, Behçet syndrome, chronic recurrent multifocal osteomyelitis and inflammatory bowel disease among others. Autoinflammatory disorders are defined by repeating episodes or persistent fever, rash, serositis, lymphadenopathy, arthritis and increased acute phase reactants, and thus may mimic infections clinically. Most monogenic autoinflammatory syndromes present in childhood. However, because of their infrequency, diverse and nonspecific presentation, and the relatively new genetic recognition, diagnosis is usually delayed. In this article, which is Part 1 of a two-part series, the authors update monogenic autoinflammatory diseases in children with special emphasis on imaging features that may help establish the correct diagnosis.

Keywords Adenosine deaminase 2 deficiency · Autoinflammatory diseases · Children · Diagnostic imaging · Interleukin-10 · Interleukin-10 receptor deficiencies · Pyogenic arthritis pyoderma gangrenosum and acne syndrome · Sarcoidosis

Introduction

The term autoinflammation was originally used to differentiate autoimmune disorders from diseases with no specific autoantibodies or autoreactive lymphocytes that were thought to be induced by innate rather than adaptive immune dysregulation [1, 2]. However, we now know that there is overlap in the immunological characteristics of some of the autoinflammatory diseases with the classical autoimmune disorders [2].

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Autoinflammatory diseases are further divided into monogenic and polygenic autoinflammatory syndromes, depending on whether there is an identified genetic mutation. Monogenic autoinflammatory syndromes are those with identified genetic mutations and represent, for the most part, abnormal responses of innate immunity. This group includes disorders such as familial Mediterranean fever, tumor necrosis factor receptor-associated periodic syndrome (TRAPS), hyperimmunoglobulin D with periodic fever syndrome or mevalonate kinase deficiency, cryopyrin-associated periodic fever syndromes (CAPS), pyogenic arthritis pyoderma gangrenosum and acne (PAPA) syndrome, interleukin-10 and interleukin-10 receptor deficiencies, adenosine deaminase 2 deficiency and pediatric sarcoidosis. Those without an identified genetic mutation have a polygenic origin and include systemic-onset juvenile idiopathic arthritis, idiopathic recurrent acute pericarditis, Behçet syndrome, chronic recurrent multifocal osteomyelitis and inflammatory bowel disease, among others [3].

An autoinflammatory disorder should be considered in children with recurrent or persistent systemic inflammation that is not explained by other causes, such as infection or malignancy. In most cases, clinical manifestations first appear in childhood. These may include fever, rash, serositis, arthritis, meningitis, uveitis, lymphadenopathy and splenomegaly. Secondary amyloidosis can complicate long-standing disease but is exceptionally rare in childhood. Acute phase reactants are increased during disease flares and may also be abnormal between episodes. Because of the infrequency of autoinflammatory diseases, their diverse and nonspecific presentation, and the relatively new genetic recognition, diagnosis is usually delayed.

In Part 1 of this series, we review monogenic autoinflammatory diseases, focusing on entities that are more pertinent to pediatric radiologists. Although we highlight the most relevant imaging features that may help establish the correct diagnosis, most of the imaging findings are nonspecific and categorization into a definite entity is not always possible. However, delineating organ involvement is more important than diagnostic labels and imaging examinations are particularly useful in this regard.

Periodic fever syndromes

Fever is a frequent flag for sickness in children and is usually caused by infection. However, once infection has been excluded, rheumatological diseases and malignancy should be considered. Relatively frequent peaks of fever of unknown origin combined with specific symptoms are classified as recurrent or periodic fever syndromes, which are listed in Table 1.

Familial Mediterranean fever

Familial Mediterranean fever is the most common monogenic autoinflammatory disorder [4]. It has an autosomal recessive pattern of inheritance, due to genetic alterations in the *MEFV* gene located on chromosome 16 [4, 5]. *MEFV* generates the protein pyrin, which is a mediator implicated in several autoinflammatory disorders that participates in the innate immune system and regulates the production of interleukin-1β [6].

Familial Mediterranean fever is more common among non-Ashkenazi Jews, Arabs, Armenians and Turks [6]. The diagnosis is made on the basis of recurrent brief episodes of fever and abdominal, thoracic, articular or cutaneous manifestations with no recognizable infection. Mediterranean origin, positive family history, beginning of the symptoms in childhood or adolescence and good response to colchicine favor the diagnosis. Furthermore, genetic analysis is an additional useful diagnostic tool.

The main cause of painful recurrent abdominal attacks in familial Mediterranean fever is peritonitis, which is a nonspecific presentation and more frequently secondary to other causes of acute abdomen that need to be excluded before familial Mediterranean fever is considered in the differential diagnosis (Table 2). Abdominal imaging findings include signs of paralytic ileus, hepatosplenomegaly, ascites, mesenteric/peritoneal thickening, retroperitoneal inflammation and fibrosis, and lymphadenopathy, including retroperitoneal lymphadenopathy (Figs. 1, 2, 3) [7–9]. Bowel wall thickening is also seen occasionally and is believed to be secondary to focal peritonitis. It may also be due to familial Mediterranean fever-associated diseases such as inflammatory bowel disease and Henoch-Schönlein purpura, as well as to secondary amyloidosis, which is extremely rare in children because it only occurs after long-standing inflammation [10].

Chest pain may be due to inflammation of the pleura or referred pain from subdiaphragmatic inflammation. Chest radiographs usually show unilateral pleural effusion with or without adjacent air space disease [11]. Concomitant pericarditis with pericardial thickening and effusion can also be found [12].

Articular symptoms are frequent and may be the initial evidence of disease in pediatric patients [13]. Arthritis is commonly nonerosive, mono- or oligoarticular, and particularly affects the large joints of the lower extremities, especially knees and ankles

Table 1 Clinical and imaging features of periodic fever syndromes

	Familial Mediterranean fever	Tumor necrosis factor receptor-associated periodic syndrome	Hyperimmunoglobulin D/mevalonate kinase deficiency	Cryopyrin-associated periodic fever syndromes		
				Familial cold autoinflammatory syndrome	Muckle–Wells syndrome	Neonatal-onset multisystem inflammatory disease
Abdominal	Paralytic ileus Hepatosplenomegaly Ascites Peritoneal thickening Retroperitoneal fibrosis	Ascites Peritoneal thickening Bowel wall thickening	Hepatomegaly Splenomegaly			Hepatomegaly Splenomegaly
Cardiopulmonary	Pleural and pericardial effusions	Pleural and pericardial effusions				
Musculoskeletal	Arthritis, monoarthritis or oligoarthritis of large joints in lower extremities Spondyloarthropathy	Muscular edema Fasciitis Subcutaneous inflammation Mono or oligoarthritis	Arthritis, usually polyarticular involving large joints	Polyarthralgia	Arthritis, affecting predominantly large joints	Bizarre enlargement of the ossified portion of the physes
Neurological			In mevalonic aciduria, white matter T2 hyperintense foci and cerebellar atrophy on MRI		Sclerosis-like lesions on MRI involving the periventricular area and the corpus callosum	Cerebral atrophy Calcifications of the falx cerebri and dura mater Leptomeningeal enhancement and chronic cochlear inflammation
Lymphadenopathy	Can be present	Can be present	Can be present		Can be present	
Other distinctive features	Fever, rash	Conspicuous eye and skin symptoms, recurrent infections, fever	Fever, skin rash, headaches, recurrent infections	Chronic urticaria, cold induced rash, conjunctivitis	Familial deafness, rash, conjunctivitis	Familial deafness, rash

MRI magnetic resonance imaging

[11, 14, 15]. The main musculoskeletal imaging findings include joint effusion, synovial thickening and enhancement, tenosynovitis, enthesopathy and cellulitis (Figs. 4, 5).

Inflammation of the tunica vaginalis, which is an extension of the peritoneum, may lead to acute scrotal pain. Testicular ultrasound (US) may show unilateral epididymal and testicular enlargement, scrotal skin thickening and hydrocele. In addition, Doppler US is very helpful in the differential diagnosis with other causes of acute scrotum, particularly with testicular torsion, showing increased or normal testicular perfusion in children with acute scrotal pain [16] (Table 3).

Colchicine is the preferred treatment to prevent fever and systemic amyloidosis [17].

Tumor necrosis factor receptor-associated periodic syndrome

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is the second most frequent hereditary periodic fever disease. It has an autosomal dominant inheritance and is induced by mutations in the *TNFRSF1A* gene, which generates the tumor necrosis factor receptor [18]. TRAPS may present at any age, including in infants, and does not have a predilection for specific ethnicities [4].

Clinical presentation resembles that of familial Mediterranean fever and other periodic fever syndromes, systemic-onset juvenile idiopathic arthritis, Behçet disease, and PAPA syndrome, with febrile episodes, serositis, and

Table 2 Sonographic differential diagnosis of abdominal attacks in familial Mediterranean fever

Entity	Imaging findings
Familial Mediterranean fever	Paralytic ileus Ascites Increased echogenicity of the mesentery and/or retroperitoneum Lymphadenopathy Hepatosplenomegaly Bowel wall thickening
Acute appendicitis	Aperistaltic, non-compressible, hyperemic, dilated appendix (>6 mm outer diameter) Hyperechoic appendicolith with posterior acoustic shadow Increased echogenicity of the periappendiceal fat Periappendiceal fluid collection Mesenteric lymphadenopathy
Intussusception	Doughnut sign given by multiple concentric rings of intussuscepted bowel on axial images with internal hyperechoic crescent-shape structure representing intussuscepted mesentery (crescent-in-doughnut sign) Pseudokidney or sandwich sign given by intussuscepted bowel and mesentery on longitudinal images
Small bowel obstruction	Multiple fluid-filled dilated bowel loops (diameter >2.5 cm) with decreased motility, proximal to a collapsed bowel segment
Acute cholecystitis	Cholelithiasis Gallbladder wall thickening (>3 mm) Pericholecystic fluid Gallbladder distension Gallbladder sludge
Acute pyelonephritis	Focal or diffuse renal enlargement Areas of increased or decreased parenchymal echogenicity Loss of corticomedullary differentiation Urothelial thickening
Acute pancreatitis	Focal or diffuse pancreatic enlargement Peripancreatic fluid
Pelvic inflammatory disease	Intraperitoneal fluid Thickening and increased vascularity of the endometrium Adnexal mass with heterogeneous echotexture Dilated fallopian tubes Echogenic fluid in the tube (pyosalpinx)

articular and cutaneous manifestations. Distinctive features of TRAPS are conspicuous eye and skin symptoms, and longer attacks [18]. Polyserositis is more frequent but isolated pericarditis can occur, too (Fig. 6). Abdominal pain with tenderness resembling an acute abdomen may be due to peritonitis or inflammation of the abdominal wall musculature [19]. Ascites, retroperitoneal and mesenteric lymphadenopathy, chronic inflammation and fibrosis of the peritoneum, bowel

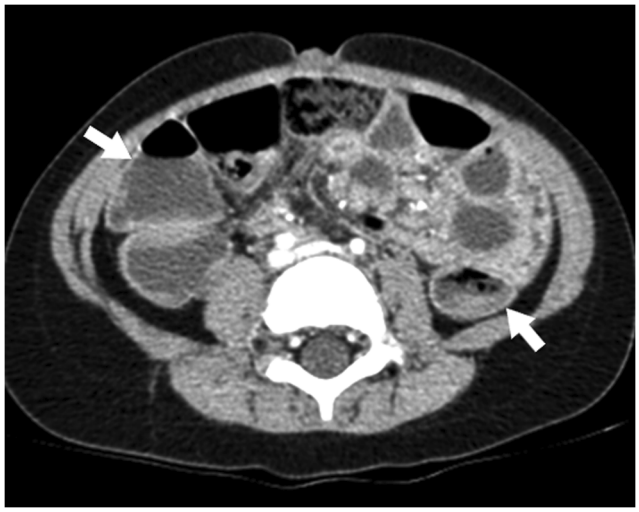

Fig. 1 Familial Mediterranean fever in a 2-year-old girl with abdominal pain for 2 months. Axial contrast-enhanced CT image of the abdomen shows diffuse dilatation of small and large bowel loops with air-fluid levels in keeping with paralytic ileus (*arrows*). Lack of a transition point helped in the differentiation from small bowel obstruction. There were no inflammatory changes in the remainder of the abdomen

obstruction due to adhesions, inflammation of the small bowel, and ulcerations in the duodenum, small intestine and colon have been reported in the literature (Fig. 7) [19, 20]. Articular involvement is generally monoarticular or oligoarticular, most commonly involving the knees, shoulders, elbows, hips, fingers, wrists and temporomandibular joints [21, 22]. Magnetic resonance imaging (MRI) may reveal underlying muscular edema, fasciitis and subcutaneous edema as increased T2

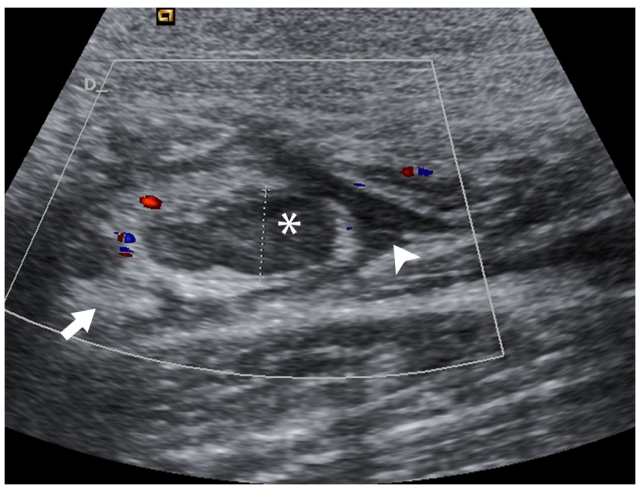

Fig. 2 Familial Mediterranean fever in a 6-year-old girl with fever and abdominal pain. Transverse abdominal sonogram of the abdomen shows lymphadenopathy (*asterisk*), as well as thickening, hyperechogenicity and hyperemia of the mesentery (*arrow*), associated with a small amount of free fluid (*arrowhead*). In this setting, differential diagnosis includes other causes of acute abdomen, such as acute appendicitis

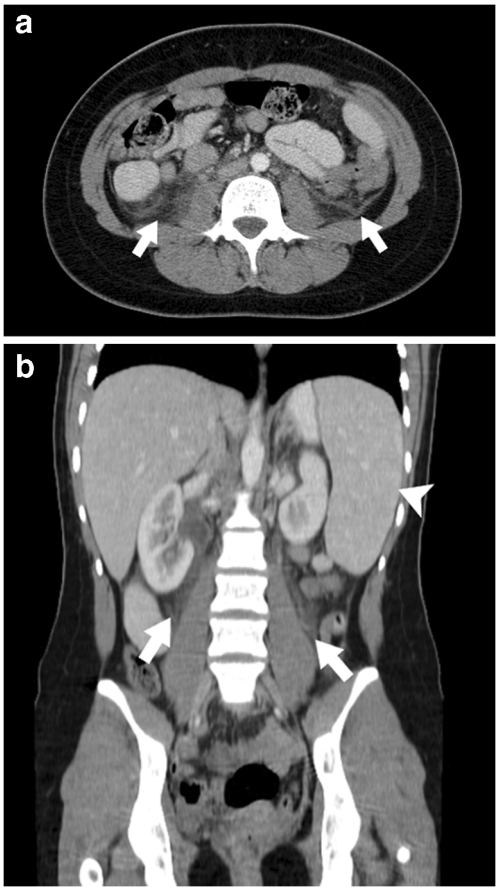

Fig. 3 Familial Mediterranean fever in a 16-year-old girl with abdominal pain and vomiting. Axial (**a**) and coronal (**b**) contrast-enhanced CT images of the abdomen show a small amount of fluid and stranding of the fat in the retroperitoneum extending into the perinephric fat and into the paracolic gutters bilaterally in keeping with inflammatory changes in the retroperitoneum (*arrows*). Note also splenomegaly (*arrowhead* in **b**). Although rare in children, the differential diagnosis includes retroperitoneal fibrosis, which presents with fibrous tissue that envelops the great vessels and ureters with associated hydronephrosis, which can be idiopathic or secondary to prior surgery, malignancy, infection, autoimmune diseases (such as systemic lupus erythematosus or juvenile idiopathic arthritis) and drugs

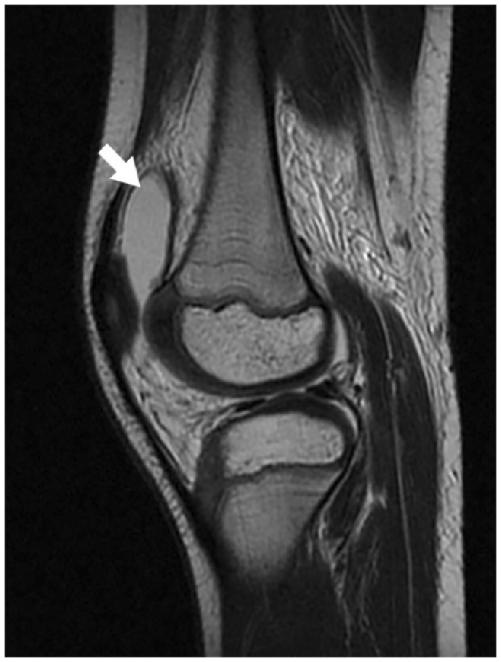

Fig. 4 Familial Mediterranean fever in an 8-year-old boy with knee pain. Sagittal T2-weighted MRI of the knee shows a moderate-size joint effusion (*arrow*). Arthritis in familial Mediterranean fever and tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is usually nonerosive and monoarticular or oligoarticular. The absence of muscular edema and fasciitis on MRI helps in the differentiation from TRAPS

signal intensity within these areas [23, 24], representing the most distinctive imaging features of TRAPS.

The diagnosis of TRAPS is achieved with genetic testing [18]. Treatment depends on the severity of the manifestations. Children with occasional episodes may be treated with prednisone during the attacks, while in children with more frequent episodes, etanercept, an anti-tumor necrosis factor, may be effective in preventing the attacks. Anakinra (interleukin-1 receptor antagonist) and canakinumab (anti-interleukin-1 antibody) may also be beneficial in some children [4].

Hyperimmunoglobulin D syndrome/mevalonate kinase deficiency

Hyperimmunoglobulin D syndrome/mevalonate kinase deficiency results from autosomal recessive mutations in the *MVK* gene, which encodes mevalonate kinase, an important enzyme involved in the biosynthesis of nonsterol isoprenoid [25]. The mildest presentation of the disease known as hyperimmunoglobulin D syndrome is caused by decreased mevalonate kinase activity, while the more severe mevalonic aciduria is caused by lack of enzymatic activity [26].

Hyperimmunoglobulin D syndrome is defined by repeating febrile episodes, lymphadenopathy, hepatosplenomegaly, abdominal pain, and articular and cutaneous manifestation with onset in infancy [27]. Crises may be triggered by vaccination, infection, surgery, trauma and stress [28]. Some children present with a nondestructive arthritis, most frequently affecting the large joints and with a polyarticular distribution. Lymphadenopathy is more frequent in patients with hyperimmunoglobulin D syndrome than in familial Mediterranean fever [28].

Headache is the most frequent and often the only neurological symptom. However, some children present with developmental delay, ataxia, ocular symptoms and seizures, demonstrating the clinical continuum between mevalonic aciduria and hyperimmunoglobulin D syndrome [29]. MRI may demonstrate T2 hyperintensities in the white matter [30], cerebral atrophy, and more characteristically cerebellar atrophy (Fig. 8) [31, 32].

Although clinical findings, and serum IgD and urinary mevalonic aciduria analysis are useful for diagnosis, confirmation is

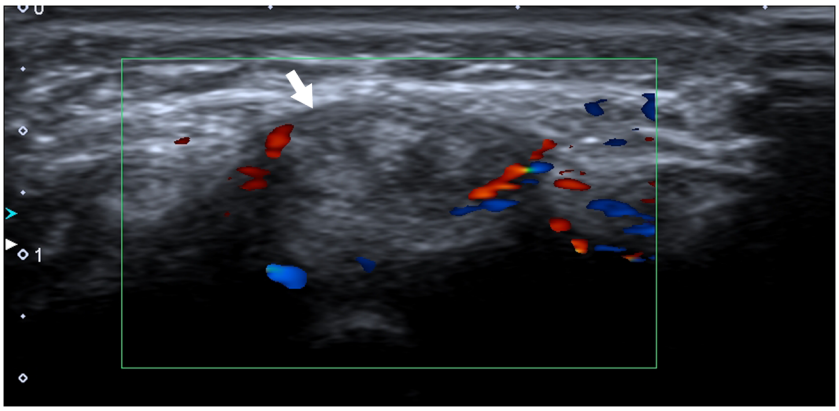

Fig. 5 Familial Mediterranean fever in a 14-year-old boy with carpal pain. Transverse color Doppler sonogram shows thickening and hyperemia of the extensor digitorum tendon sheath (*arrow*), in keeping with tenosynovitis

established with genetic testing. Blockade of interleukin-1 with anakinra or canakinumab is useful in most patients [33].

Table 3 Sonographic differential diagnosis of acute scrotal pain in familial Mediterranean fever

Entity	Imaging findings
Familial Mediterranean fever	Unilateral epididymal and testicular enlargement with normal or increased vascularity on Doppler interrogation Scrotal skin thickening Hydrocele
Testicular torsion	Twisting of the spermatic cord Redundant spermatic cord Horizontal position of the testis Absent or decreased intratesticular blood flow Flow can be increased after detorsion Enlargement of the testis Heterogeneous echotexture of the testis Epididymal enlargement without hyperemia Hydrocele
Torsion of testicular appendage	Round extra-testicular mass with high or mixed echogenicity and no internal vascularity Enlarged epididymis Hydrocele Scrotal wall thickening.
Acute epididymitis	Enlargement of the epididymis Altered echotexture of the epididymis Increased blood flow in the epididymis, testis or both Scrotal wall thickening Hydrocele
Idiopathic scrotal edema	Thickening of the scrotal wall and hypervascularity Normal-appearing testes
Henoch-Schönlein purpura	Epididymal enlargement, more frequently bilateral Usually normal-appearing testes with normal intratesticular blood flow Scrotal wall thickening Hydrocele

Cryopyrin-associated periodic fever syndrome

Cryopyrin-associated periodic fever syndrome (CAPS) is a family of syndromes resulting from mutations in the *C1AS1* gene, now known as *NLRP3*, on chromosome 1 [34]. Familial cold autoinflammatory syndrome and neonatal-onset multisystem inflammatory disease (NOMID) represent the two ends of a spectrum of disease activity. Children usually develop symptoms early in life with fever, cutaneous and articular manifestations.

Familial cold autoinflammatory syndrome

Familial cold autoinflammatory syndrome has an autosomal dominant inheritance and is typified by repeated brief febrile episodes, rash, polyarthralgia and conjunctivitis triggered by cold [35]. No specific imaging findings have been described in this entity.

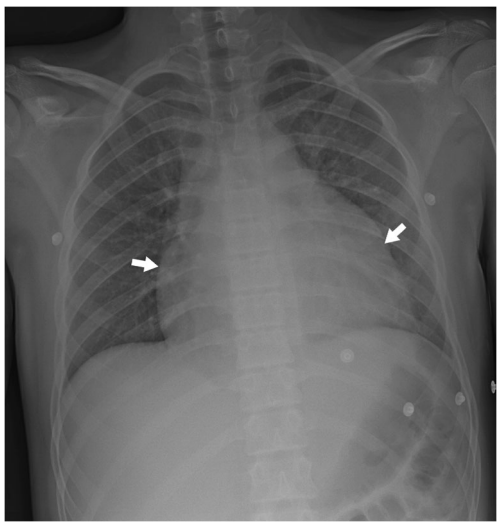

Fig. 6 Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) in a 5-year-old boy with fever and dyspnea. Posteroanterior chest radiograph shows cardiac enlargement with a "water-bottle" configuration (*arrows*) that corresponded to pericardial effusion on echocardiography (not shown)

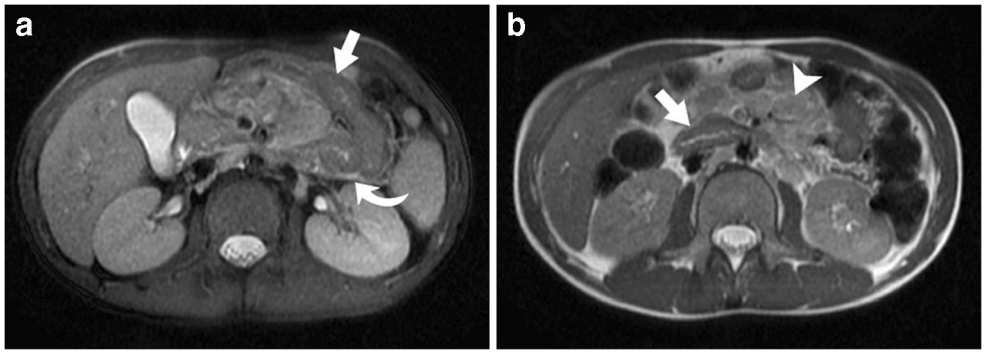

Fig. 7 Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) in an 11-year-old boy with fever, abdominal and musculoskeletal pain. Axial fat-suppressed T2-weighted (**a**) and axial T2-weighted MRI (**b**) of the abdomen show segments of small bowel wall thickening (*straight arrows*), mesenteric and retroperitoneal lymphadenopathy (*arrowhead* in **b**), and trace of free intraperitoneal fluid (*curved arrow* in **a**). Although clinical presentation mimicked acute appendicitis, the imaging differential diagnosis favored inflammatory bowel disease, Behçet disease and Henoch-Schönlein purpura, among others

Muckle–Wells syndrome

This is most commonly an autosomal dominant disorder, although sporadic cases may also happen. Recurrent febrile episodes with cutaneous, articular and ocular manifestations are characteristic. Fever is not always present [4, 36]. Joint involvement is usually in the form of oligoarthritis, predominantly affecting large joints. Sensorineural hearing loss is also common. Other neurological abnormalities are less common but multiple sclerosis-like lesions involving the periventricular area and the corpus callosum have been described on MRI in these patients [37]. Lymphadenopathy, abdominal pain and headache have been described as well (Fig. 9). Triggering factors are not commonly recognized.

Neonatal-onset multisystem inflammatory disease

Neonatal-onset multisystem inflammatory disease (NOMID), also called chronic infantile neurological cutaneous and articular syndrome, is associated with the most severe CAPS phenotype. Most cases of NOMID are sporadic, with only a minority having an autosomal dominant inheritance [38].

Children usually show cutaneous and articular manifestations, with fever at birth or in the first years of life [4]. However, fever may be absent. Osseous and articular inflammation may vary from arthralgia to severe arthropathy secondary to anomalous endochondral ossification and bony overgrowth [39]. Articular involvement is usually asymmetrical and mainly affects the knees. The initial imaging finding is physeal widening, with subsequent development of fraying and cupping of the metaphysis, which is irregular in outline, simulating rickets [40]. The characteristic radiographic finding is an unusual hypertrophy of the ossified part of the growth cartilage, appearing as a heterogeneous calcified mass with associated deformity of the adjacent epiphysis and metaphysis. The enlarged physis appears hypointense on T1- and T2-weighted images, and shows enhancement following intravenous contrast injection (Fig. 10) [40]. Decreased bone

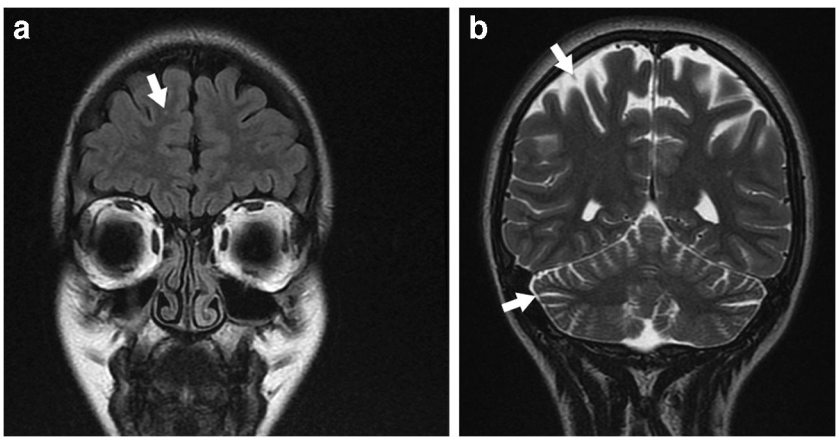

Fig. 8 Hyperimmunoglobulin D syndrome in an 18-year-old girl who presented with headache and pyramidal signs. **a** Coronal fluid-attenuated inversion recovery (FLAIR) MRI of the brain shows a non-specific subcortical focus of high signal intensity (*arrow*), a finding that has been described in patients with chronic headache in this entity. **b** Coronal T2-weighted MRI of the brain shows supra- and infratentorial parenchymal volume loss (*arrows*)

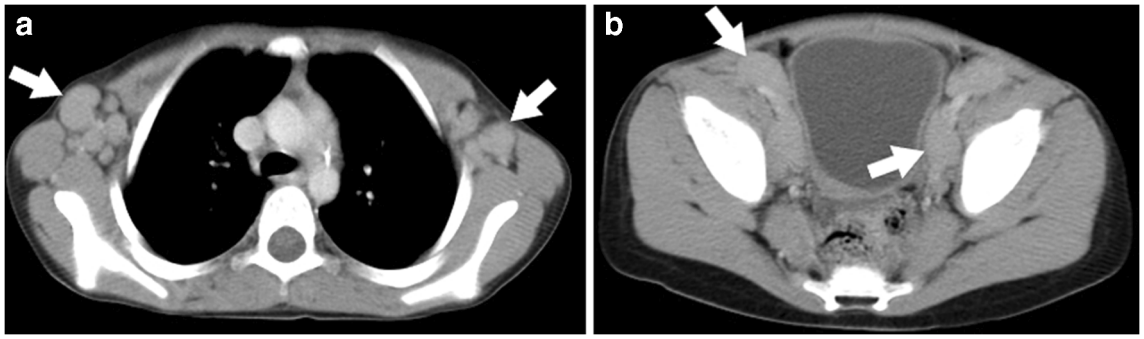

Fig. 9 Muckle-Wells syndrome (V200 M mutation in *C1AS1* gene) in a 4-year-old girl with an 8-month history of rash, fatigue, decreased appetite and palpable enlarged lymph nodes. Axial contrast-enhanced CT images of the chest (**a**) and pelvis (**b**) show extensive bilateral axillary and iliac lymphadenopathy (*arrows*). Differential diagnosis includes other periodic inflammatory disorders, systemic-onset juvenile idiopathic arthritis, Behçet disease and lymphoproliferative disorders

mineralization, conspicuous subperiosteal new bone formation along the diaphysis and metaphysis of the involved long bones, delayed bone age, genu varus or valgus, and leg length discrepancy may also be seen [4, 41, 42]. The differential

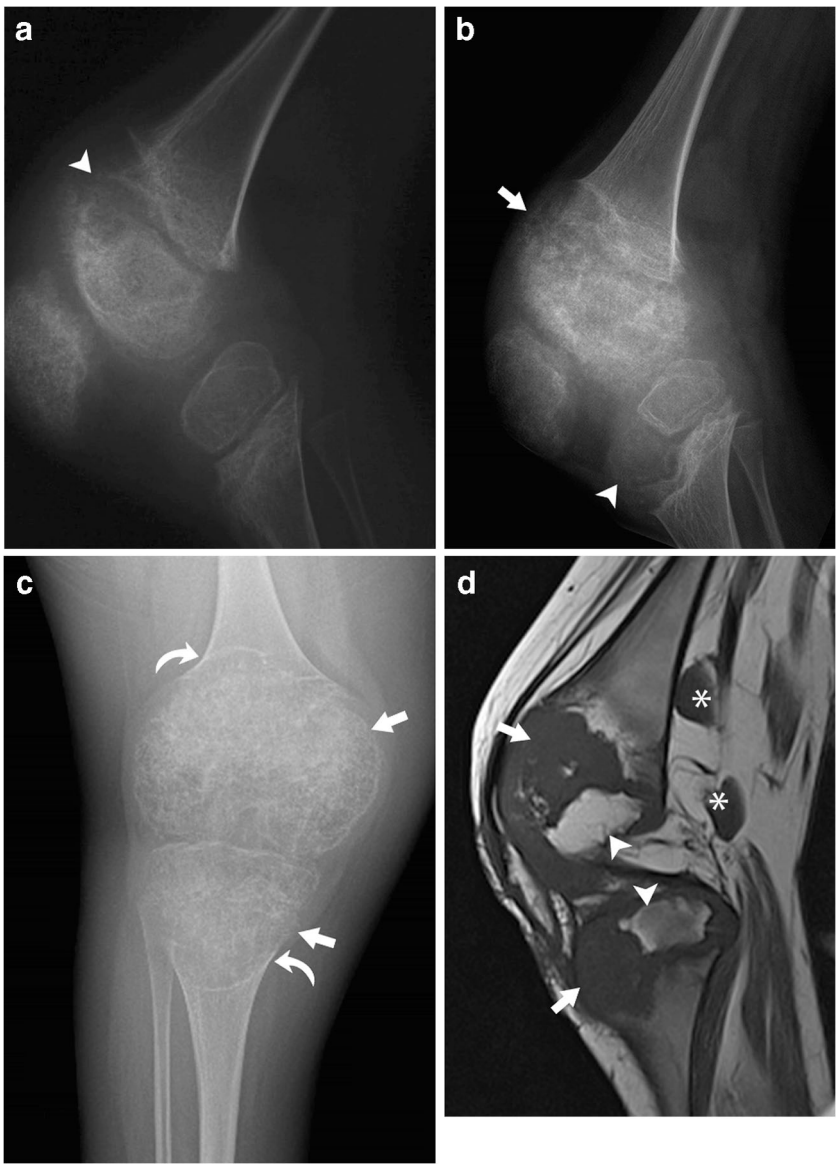

Fig. 10 Neonatal-onset multisystem inflammatory disease (NOMID) in a 13-year-old boy with recurrent fever, urticaria and right ankle and knee pain. **a** Lateral radiograph of the right knee at 8 years of age shows widening of the anterior aspect of the distal femoral physis with focal indentation of the adjacent epiphysis (*arrowhead*). **b** Lateral radiograph of the right knee 2 years later shows partial calcification of the enlarged distal femoral physis (*arrow*) and new widening of the anterior aspect of the proximal tibial physis by an unossified mass (*arrowhead*). **c** Anteroposterior radiograph 3 years later shows the progression of the ossification and physeal/epiphyseal enlargement at the distal femur and proximal tibia (*straight arrows*), and cupping of the distal femoral and proximal tibial metaphyses with sclerotic margin (*curved arrows*). **d** Sagittal T1-weighted MRI of the right knee shows hypointense enlargement of the distal femoral and proximal tibial physes (*arrows*) with associated deformity of the adjacent epiphyses (*arrowheads*) and prominent popliteal lymph nodes (*asterisks*)

Table 4 Imaging differential diagnosis of neonatal-onset multisystem inflammatory disease (NOMID)

Entity	Imaging findings
NOMID	Hypertrophy of the ossified part of the growth cartilage
	Deformity of the adjacent epiphysis
	Fraying and cupping of the metaphysis
	Subperiosteal new bone formation along the diaphysis and metaphysis of the involved long bones
	Decreased bone mineralization
	Most common: asymmetrical involvement of the knees
Rickets	Physeal widening and abnormal configuration of the metaphysis:
	• Fraying: indistinct margins of the metaphysis
	• Splaying: widening of metaphyseal ends
	• Cupping: concavity of metaphysis
	Most common: distal femur, proximal tibia, distal ulna and anterior rib ends (rachitic rosary)
Chronic recurrent multifocal osteomyelitis	Lytic and sclerotic metaphyseal lesions
	Common location: pelvis, lower extremities, clavicle, shoulders and spine
	Frequent involvement of the physis in tubular bones, but the lesion is centered in the metaphysis rather than the epiphysis or physis
Systemic-onset juvenile idiopathic arthritis	Primary involvement of the synovium resulting in synovial thickening and enhancement
	Tenosynovitis
	Joint effusion
	Bone marrow edema
	Juxta-articular osteopenia
	Joint space narrowing
	Bone erosions
	Growth abnormalities
	Bone ankylosis
Tuberculosis	Spondylodiscitis
	• Most frequent site of involvement
	• Subligamentous spread may lead to multiple levels of involvement
	• Intervertebral disc is initially preserved
	• Paravertebral or epidural masses are common
	Arthritis
	• Usually monoarticular
	• Hips and knees most frequently involved
	• Joint effusion, periarticular osteopenia, cortical irregularity, lytic lesions, subperiosteal new bone formation and decrease in joint space
	Osteomyelitis
	• Skull, hands, feet and ribs are most commonly involved
	• Usually well-defined lytic lesions with or without marginal sclerosis and sequestrum
	• Expansion of the bones and honeycombing may be seen

diagnosis of the musculoskeletal findings of NOMID include rickets, chronic recurrent multifocal osteomyelitis, systemic-onset juvenile idiopathic arthritis and tuberculosis (Table 4).

Neurological manifestations are common. Computed tomography (CT) and MRI may show mild prominence of the ventricles and increased extra-axial fluid, suggestive of mild cerebral atrophy [36], as well as calcifications of the falx cerebri and dura mater, leptomeningeal enhancement and cochlear inflammation [4, 43].

Interleukin-1 targeted therapies appear to be useful including anakinra, rilonacept and canakinumab [44, 45].

Table 5 Differential diagnosis of monogenic autoinflammatory diseases other than periodic fever syndromes

	Pyogenic arthritis pyoderma gangrenosum and acne (PAPA) syndrome	Interleukin-10/interleukin-10 receptor deficiency	Adenosine deaminase 2 deficiency	Pediatric sarcoidosis
Musculoskeletal	Most common: destructive oligoarthritis involving the appendicular skeleton	Arthritis		Tenosynovitis >> intraarticular synovitis Camptodactyly Carpal crowding Biconcave intra-articular surface of the distal radius Plump and short ulna Long thin diaphysis of the second metacarpal Rotation and pseudo-collapse of the lunate and scaphoid
Gastrointestinal		Severe early-onset inflammatory bowel disease with abscesses, anal fissures, and enterocutaneous and rectovaginal fistulae		
Neurological			Lacunar infarctions and hemorrhages in the brainstem and deep brain nuclei	
Others		Recurrent respiratory diseases	Hepatosplenomegaly Portal hypertension	Renal, pulmonary, parotid and lymph node involvement

Pyogenic arthritis pyoderma gangrenosum and acne syndrome

PAPA syndrome is an infrequent autoinflammatory disease inherited in an autosomal dominant pattern secondary to genetic alterations in the proline serine threonine phosphatase-interacting protein 1 (*PSTPIP1/CD2BP1*) gene, resulting in overproduction of interleukin-1β [4, 46].

PAPA syndrome usually presents early in life with arthritis, cystic acne, pyoderma gangrenosum and pathergy-like sterile

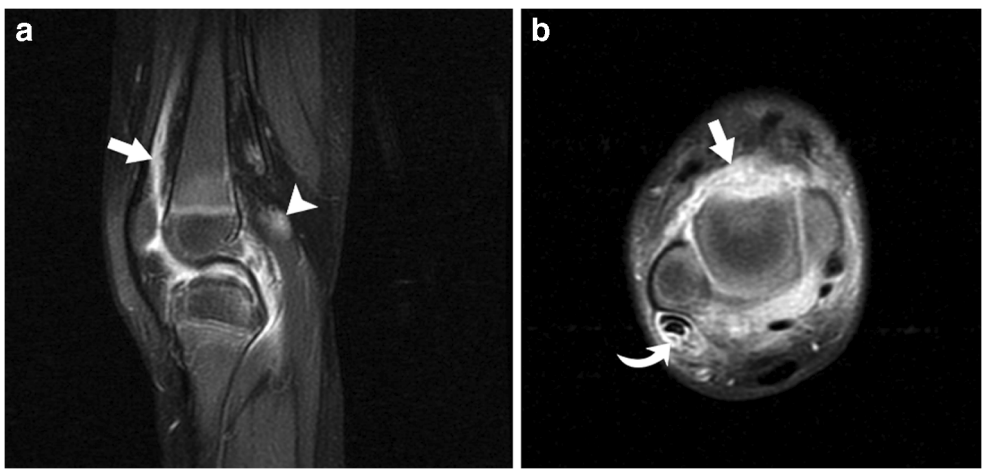

Fig. 11 Pyogenic arthritis pyoderma gangrenosum and acne (PAPA) syndrome in a 2-year-old girl with slowly evolving right knee and ankle arthritis. **a** Sagittal contrast-enhanced fat-suppressed T1-weighted MRI of the right knee shows thickening and enhancement of the synovium (*arrow*) and reactive popliteal lymph node (*arrowhead*), in keeping with active synovitis. **b** Axial fat-suppressed T2-weighted MRI of the right ankle shows increased signal intensity in the tibiotalar joint that may represent effusion and/or synovial thickening (*straight arrow*), and tenosynovitis of the peroneal tendons (*curved arrow*)

abscesses at injection sites (Table 5). Arthritis is usually oligoarticular and destructive, mainly affecting the appendicular skeleton, including the elbow, knee, ankle and wrist (Fig. 11). Radiographic findings include osteophyte formation, generalized joint narrowing, subchondral sclerosis and cysts, periostitis and, less frequently, ankylosis [47, 48]. Osteolytic bone lesions, similar to those described in deficiency of interleukin-1 receptor antagonist and chronic recurrent multifocal osteomyelitis have also been described [49]. MRI findings are nonspecific, although they may show large joint effusions, synovial thickening and hyperenhancement, bone marrow edema and inflammatory changes in the soft tissues [47].

Diagnosis at presentation may be tricky as clinical and imaging findings may mimic septic arthritis, osteomyelitis, juvenile idiopathic arthritis or chronic recurrent multifocal osteomyelitis (Table 6). In the setting of recurrent or chronic manifestations, other monogenic autoinflammatory disorders have to be included in the differential diagnosis. Therefore, clinical, laboratory and genetic findings should be put together to diagnose PAPA syndrome, which has to be considered in afebrile patients with history of recurrent joint inflammation, particularly after minor trauma, with purulent but aseptic synovial fluid [47]. Glucocorticoids are standard treatment, although etanercept, an anti-tumor necrosis factor and interleukin-1 antagonist, appears promising [50].

Interleukin-10 and interleukin-10 receptor deficiencies

Interleukin-10 and interleukin-10 receptor deficiencies are rare entities secondary to loss-of-function mutations in the genes encoding interleukin-10 or interleukin-10 receptor [50]. Clinical manifestations commonly begin early in life with inflammatory bowel disease, particularly with severe perianal involvement [51, 52] (Fig. 12). Other findings, such as folliculitis, recurrent respiratory disease, and arthritis, may also be present [53] (Table 5).

Interleukin-10 and interleukin-10 receptor deficiencies are characterized by a severe course with multifocal involvement, including abscesses, anal fissures and enterocutaneous and rectovaginal fistulae, usually requiring surgery [51]. Abdominal US may show bowel wall thickening and hyperemia with abnormal echogenicity and contours as well as increased echogenicity of the surrounding fat and abscess formation. Pelvic MRI is very useful in evaluating perianal disease as it allows precise delineation of fistulous tracts and identification of secondary fistulas or abscesses. The protocol used at our institution includes coronal short-TI inversion recovery and T1-weighted sequences, oblique axial fat-suppressed T2-weighted and diffusion, sagittal fat-suppressed T2-weighted, and oblique coronal and axial contrast-enhanced fat-suppressed T1-weighted

Table 6 Imaging differential diagnosis of pyogenic arthritis pyoderma gangrenosum and acne (PAPA) syndrome (modified from [47])

	Joint effusion	Synovial thickening and enhancement	Soft-tissue edema	Abscess formation	Bone marrow edema	Periostitis	Subperiosteal abscess	Chondral injury/destruction	Rice bodies	Juxta-articular osteoporosis	Subchondral erosions	Decreased joint space	Bone ankylosis
Pyogenic arthritis pyoderma gangrenosum and acne (PAPA) syndrome	+++	+++	+++	–	+++	±	–	+++	–	+	–	+++	+++
Septic arthritis	+++	+++	+++	+++	+++	+++	–	+++	+	+++	–	+++	++/+++
Juvenile idiopathic arthritis	+++	+++	+++	–	+/++	++	–	+++	++/+++	++	+++	+++	+++
Osteomyelitis	+/++	+	+++	+++	+++	+++	+++	++	–	–	–	++	++
Chronic recurrent multifocal osteomyelitis	++	++	+++	+	+++	+++	++	+	–	–	–	+	+

– Not present
± Rare
+ Occasionally present
++ Fairly frequent
+++ Very frequent

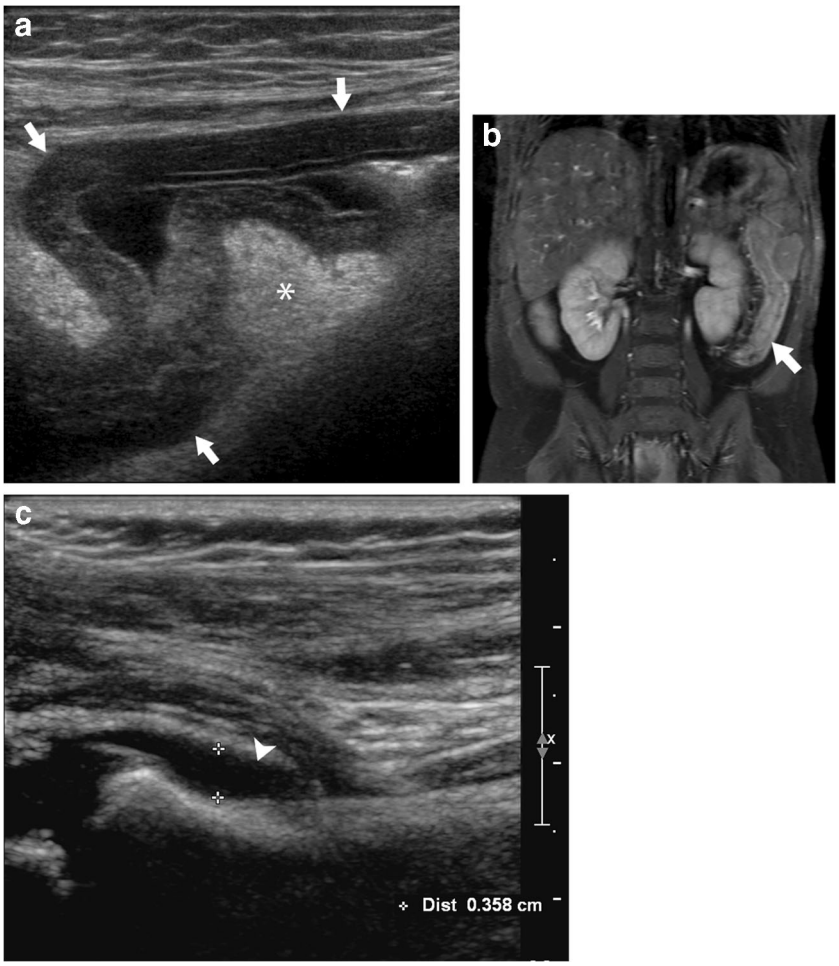

Fig. 12 Interleukin-10 receptor mutation leading to interleukin-10 receptor alpha deficiency in a 13-month-old girl who presented with colitis, polyarthritis, rash and recurrent infections. **a** Transverse sonogram of the abdomen shows marked wall thickening of the sigmoid colon (*arrows*) with increased echogenicity of the surrounding fat (*asterisk*). **b** Coronal contrast-enhanced fat-suppressed T1-weighted MRI of the abdomen shows diffuse wall thickening and enhancement of the descending colon (*arrow*). **c** Longitudinal sonogram of the right hip shows moderate-size anechoic joint effusion (*arrowhead* and *between calipers*)

sequences. Oblique axial and coronal images should be oriented orthogonal and parallel to the anal canal.

Remarkably, children show no response to immunosuppressive treatment, but allogeneic hematopoietic stem cell transplantation appears to lead to sustained remission [51, 54].

Adenosine deaminase 2 deficiency

Adenosine deaminase 2 deficiency is a recessive inherited autoinflammatory disease secondary to loss-of-function mutations in cat eye syndrome chromosome region 1 (*CECR1*), which generates an enzyme named adenosine deaminase type

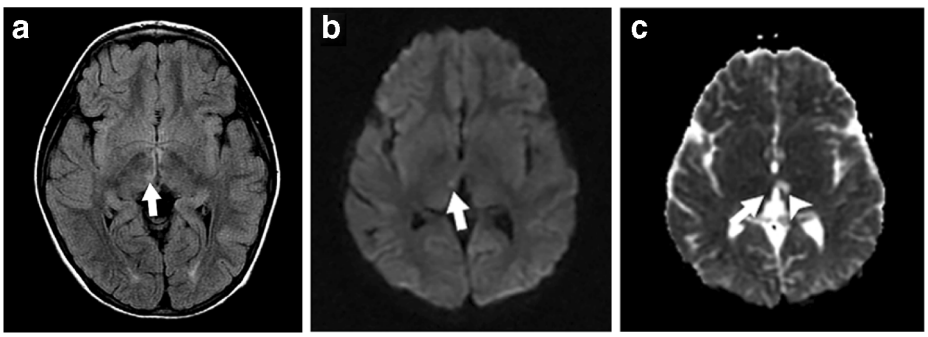

Fig. 13 Deficiency of adenosine deaminase 2 in a 5-year-old boy with an 1-week history of diplopia and unsteady gait. **a** Axial fluid-attenuated inversion recovery MRI of the brain shows a hyperintense focus in the right medial thalamus (*arrow*). **b**, **c** Axial diffusion-weighted (**b**) and axial apparent diffusion coefficient map (**c**) of the brain show diffusion restriction of the abnormality seen in (**a**) appearing as a hyperintense focus in (**b**) (*arrow*) and a hypointense focus in (**c**) (*arrow*), consistent with an acute arterial ischemic stroke. An old infarct is also noted in the left medial thalamus in (**c**) (*arrowhead*)

2 involved in the maintenance of vascular endothelium and the development of monocytes [55, 56]. Affected patients can develop both vascular disease and immunodeficiency (Table 5).

Symptoms are mainly secondary to the involvement of medium- and small-sized arteries and vary greatly depending on the respective organ or system affected [56]. The most frequent presentation is early onset stroke, particularly before 5 years of age (Fig. 13), and the polyarteritis nodosa phenotype. In fact, adenosine deaminase 2 deficiency should be considered in children with stroke even if there is no evidence of systemic inflammation or cerebral vasculitis, as well as in patients with known polyarteritis nodosa and central nervous system involvement**.** Typically, stroke follows systemic inflammation and primarily involves lacunar infarctions and hemorrhages in the brainstem and deep brain nuclei [57, 58]. Unenhanced head CT is often the initial study in a child presenting with possible stroke and can rule out intracranial hemorrhage. However, CT has limited sensitivity for detecting acute ischemia and stroke mimics, such as complicated migraine syndromes, focal seizures, intracranial infections and intracranial neoplasms [59]. On CT, acute lacunar infarcts appear as small ill-defined hypodensities, while chronic lacunar infarcts show a similar density to cerebrospinal fluid. MRI is the preferred imaging technique for studying a suspected stroke. On MRI, acute lacunar infarcts appear slightly hypointense on T1-weighted images, hyperintense on fluid-attenuated inversion recovery (FLAIR) and T2-weighted images and show diffusion restriction on diffusion-weighted images. Chronic lesions are isointense to cerebrospinal fluid on all sequences but may demonstrate a peripheral hyperintense rim of marginal gliosis on FLAIR and T2-weighted images. In addition, in children with adenosine deaminase 2 deficiency, cerebral angiography does not reveal typical vasculitic findings [57].

Anti-tumor necrosis factor therapy, adenosine deaminase 2-enzyme replacement therapy with fresh-frozen plasma or recombinant protein, or bone marrow transplant can be beneficial in the treatment of adenosine deaminase 2 deficiency [4, 55, 56, 60].

Pediatric sarcoidosis

Pediatric sarcoidosis is due to genetic alterations in the *NOD2* gene and encompasses a group of pediatric granulomatous inflammatory disorders characterized by early atypical skin rash, recurrent uveitis and polyarthritis with marked synovial thickening and tenosynovitis [61–63] (Table 5). Blau syndrome and early-onset sarcoidosis are, respectively, the familial and sporadic forms, with the familial cases being inherited in an autosomal dominant pattern [64].

Non-caseating epithelioid giant cell granulomas are the distinctive pathological characteristic of pediatric sarcoidosis, likely representing an excessive immune-inflammatory reaction to a persistent antigen [64].

Table 7 Imaging differential diagnosis of arthritis in pediatric sarcoidosis

	Joint effusion	Synovial thickening and enhancement	Tenosynovitis	Juxta-articular osteoporosis	Bone erosions	Camptodactyly	Involvement of peripheral joints	Involvement of the axial skeleton and temporomandibular joint	Epiphyseal growth	Periosteal thickening/ periosteal reaction
Pediatric sarcoidosis	+/++	+/++	+++ Exuberant/ "boggy"	–	–	+	+	–	–	–
Juvenile idiopathic arthritis	+++	+++	++	++	+++	–	+	+	+++	+++

– Not present
+ Occasionally present
++ Fairly frequent
+++ Very frequent

Arthritis is the most frequent manifestation and differential diagnosis with juvenile idiopathic arthritis can be challenging (Table 7). It usually develops in the first decade, often with minimal symptoms. It mostly presents as chronic nonerosive symmetrical polyarthritis affecting large and small peripheral joints, particularly wrists, knees, ankles and proximal interphalangeal joints [65]. Typically, tenosynovitis is more frequent and severe than intra-articular synovitis (Fig. 14) [66]. In fact, the flexor tendons of the digits and of the carpus, the extensor tendons of the ankle and the peroneal tendons may become very enlarged [64]. US usually reveals marked thickening of the tendon sheaths with increased vascularity on Doppler interrogation associated with synovial fluid [63]. In contrast, signs of intra-articular synovitis in the adjacent joint are not frequently present or are very mild.

Bone morphological changes may also be useful for diagnosis. They include camptodactyly, a contracture virtually limited to the proximal interphalangeal joints, carpal dysplasia with carpal crowding, loss of the normal distal radial epiphyseal anatomy with a biconcave articular surface, abnormal morphology of the distal ulna (plump ulna), short ulna, long thin diaphysis of the second metacarpal, and rotation and pseudo-collapse of the lunate and scaphoid (Fig. 13) [65].

Other clinical manifestations include interstitial pneumonitis, pericarditis, nephritis, small-vessel vasculitis, peripheral and mediastinal lymphadenopathy, cranial neuropathy and parotitis [61, 64]. Laboratory findings for pediatric sarcoidosis are nonspecific. Although elevated angiotensin converting enzyme levels may suggest sarcoidosis, the test is nonspecific in children and may be elevated in other systemic diseases. A definite diagnosis can be achieved with genetic testing. Systemic steroids, immunosuppressive and/or biological agents are the standard treatment for most children [62].

Conclusion

Imaging might provide clues for diagnosing autoinflammatory diseases but, given the wide variety and often nonspecific presentations of these diseases, its greatest value usually resides in delineating organ involvement and disease extent. Periodic fever syndromes have the articular involvement in common. However, familial Mediterranean fever and TRAPS may also cause peritonitis and pericardial and pleural effusions, while NOMID is characterized by an unusual hypertrophy of the ossified portion of the growth cartilage. PAPA syndrome is associated with a destructive arthritis. Interleukin-10 deficiency and interleukin-10 receptor deficiency syndrome should be considered in children with early-onset inflammatory bowel disease with severe perianal

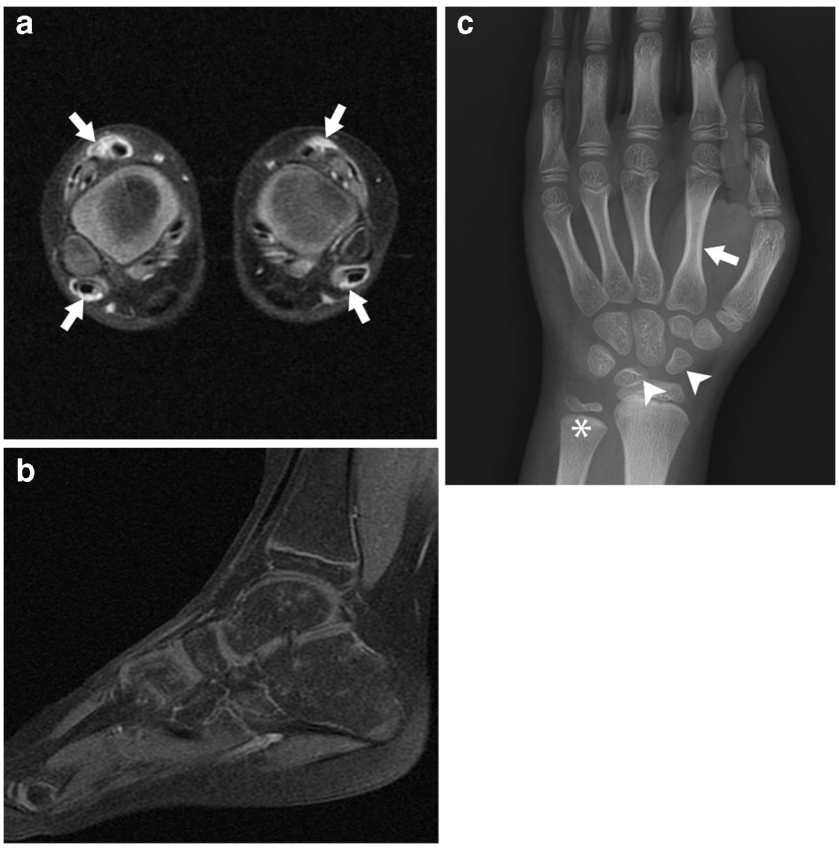

Fig. 14 Blau syndrome (familial form of pediatric sarcoidosis) in a 3-year-old girl with pain and swelling of the ankles for 2 months. **a** Axial fat-suppressed T2-weighted MRI of both ankles shows bilateral anterior tibial and peroneal tenosynovitis characterized by high T2 signal intensity fluid within the tendon sheaths (*arrows*). **b** Sagittal contrast-enhanced fat-suppressed T1-weighted MRI of the right ankle shows no evidence of articular synovitis. In children with pediatric sarcoidosis, tenosynovitis is much more frequent and severe than articular synovitis, being the best imaging clue in the differentiation from juvenile idiopathic arthritis. **c** Anteroposterior radiograph of the hand shows post-inflammatory changes including thin diaphysis of the second metacarpal bone (*arrow*), rotation and pseudo-collapse of the lunate and scaphoid (*arrowheads*), and ulnar shortening (*asterisk*)

disease. Adenosine deaminase 2 deficiency should be considered in children with stroke and in children with known polyarteritis nodosa and central nervous system involvement. Severe tenosynovitis is the most characteristic feature of pediatric sarcoidosis.

Compliance with ethical standards

Conflicts of interest None

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