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PICTORIAL ESSAY

Autoinflammatory diseases in childhood, part 2: polygenic syndromes

María Navallas[1,2,3] · Emilio J. Inarejos Clemente[1] · Estíbaliz Iglesias[4] · Mónica Rebollo-Polo[1] · Joan Calzada Hernández[4] · Oscar M. Navarro[2,3]

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Abstract

Autoinflammatory diseases are a family of disorders characterized by aberrant stimulation of inflammatory pathways without involvement of antigen-directed autoimmunity. They can be further divided in monogenic and polygenic types. 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 diseases are characterized by recurrent flares or persistent systemic inflammation and fever, as well as lymphadenopathy and cutaneous, abdominal, thoracic and articular symptoms. Although these syndromes can mimic infections clinically, the inflammatory lesions in autoinflammatory disorders are aseptic. However, because of their infrequency, varied and nonspecific presentation, and the new genetic identification, diagnosis is usually delayed. In this article, which is Part 2 of a two-part series, the authors review the main polygenic autoinflammatory diseases that can be seen in childhood, with special emphasis wherever applicable on imaging features that may help establish the correct diagnosis. However, the major role of imaging is to delineate organ involvement and disease extent.

Keywords Acute recurrent pericarditis · Autoinflammatory diseases · Behçet syndrome · Children · Chronic recurrent multifocal osteomyelitis · Inflammatory bowel disease · Systemic-onset juvenile idiopathic arthritis

Introduction

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

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 are primarily errors of innate immunity. 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 [3].

The pathogenetic mechanisms underlying autoinflammation, although still unclear and different from each other from a molecular point of view, are responsible for an aberrant activation of the immune system resulting in involvement of multiple organs and systems. Symptoms are nonspecific and include recurrent flares or persistent systemic inflammation, fever, skin rashes, chest and abdominal pain, lymphadenopathy and arthritis. Because of the rarity of autoinflammatory diseases, their varied and

✉ María Navallas
mnavallas@gmail.com

[1] Department of Radiology, Hospital Sant Joan de Déu, Passeig Sant Joan de Déu, 2, 08950 Esplugues de Llobregat, Barcelona, Spain

[2] Department of Medical Imaging, University of Toronto, Toronto, ON, Canada

[3] Department of Diagnostic Imaging, The Hospital for Sick Children, Toronto, Canada

[4] Department of Rheumatology, Hospital Sant Joan de Déu, Barcelona, Spain

nonspecific presentation, and the new genetic identification, diagnosis is usually delayed. Imaging can help provide clues for the diagnosis but the major role of imaging is to delineate organ involvement and disease extent.

In Part 2 of this series, we review the main polygenic autoinflammatory diseases in childhood, with special emphasis on imaging features that may be useful to reach the correct diagnosis.

Systemic-onset juvenile idiopathic arthritis

The systemic form of juvenile idiopathic arthritis is one of the most severe forms of juvenile idiopathic arthritis. According to the International League of Associations for Rheumatology criteria, systemic-onset juvenile idiopathic arthritis is characterized by arthritis with or preceded by at least 2 weeks of fevers that have been daily for at least 3 days, with at least one of the following: transitory rash, generalized lymphadenopathy, hepato- or splenomegaly, or serositis [4].

Arthritis, which is mandatory for a conclusive diagnosis, is not usually one of the presenting symptoms. In addition, the classical symmetrical and polyarticular joint involvement may not develop until late in the disease course [5]. Wrists, knees and ankles are frequently affected, although the hands, hips, cervical spine and temporomandibular joints can also be involved [6] (Fig. 1). Unlike the oligoarticular and polyarticular subtypes of juvenile idiopathic arthritis, the arthritis of systemic-onset juvenile idiopathic arthritis may start in the hips and can progress very rapidly, causing severe damage and dysfunction resulting in the need for early joint replacement surgery as well as loss of growth potential in younger patients. The imaging findings are summarized in Table 1. The main radiologic findings in systemic-onset juvenile idiopathic arthritis are juxta-articular osteopenia, joint space narrowing, erosions, growth abnormalities and even ankylosis (Fig. 2). Generalized delay in bone age is also common. Ultrasonography (US) is very helpful to evaluate tenosynovitis, which is common in children with polyarticular course and is characterized by increased fluid content within the tendon sheath and hypoechoic thickening of the synovial sheath with or without increased vascularity [6]. Magnetic resonance imaging (MRI) with intravenous contrast administration is the technique of choice to study arthritis [7]. It has the advantages of displaying both soft tissue and bone, being the most sensitive technique for detecting acute synovitis and tenosynovitis, and the only one able to identify bone marrow edema. Furthermore, it allows detection of changes in the joint over time and evaluates the effectiveness of therapeutic interventions. On MRI, tenosynovitis appears as increased fluid within the tendon sheath, with low or intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted images, or as increased enhancement of the tendon sheath. The most frequently affected tendons are the extensor tendons of the carpus, the flexor tendons of the fingers, the extensor tendons of the feet, and the posterior tibialis and peroneus tendons [6]. Occasionally, synovial cysts that communicate with the shoulder, elbow, wrist or knee joints are also seen [6]. Myositis is rare but can be identified by MRI [8].

Pericardial effusion is common and frequently asymptomatic, with no obvious cardiomegaly or typical electrocardiographic findings [9]. Myocarditis is much less common.

Pleural effusion, the most common chest manifestation, is frequently found incidentally on chest radiographs [6]. Interstitial lung disease, alveolar proteinosis and pulmonary hypertension are rare but are being reported with increasing frequency [10].

Lymphadenopathy and splenomegaly may occur alone or together and are characteristic of systemic-onset juvenile idiopathic arthritis (Fig. 1). Lymphadenopathy might be markedly enlarged and symmetrically distributed, especially in the cervical, axillary and inguinal regions, and thus it mimics the appearance of lymphoma [6]. Hepatomegaly is not as frequent as splenomegaly [6] (Fig. 1). Occasionally, a fatty liver can be seen secondary to glucocorticoid administration, but chronic hepatic disease generally does not occur.

Acute neurological episodes such as macrophage activation syndrome and posterior reversible encephalopathy syndrome are uncommon but serious complications in children with systemic-onset juvenile idiopathic arthritis [6]. Macrophage activation syndrome is an acute, life-threatening condition characterized by pancytopenia, disseminated intravascular coagulopathy, hepatic dysfunction and persistent fever resulting in multiorgan failure. Brain MRI may show intracranial hemorrhages and cerebral edema [11]. Posterior reversible encephalopathy syndrome consists of a neurotoxic state secondary to the inability of the circulation to autoregulate in response to acute changes in blood pressure [12]. MRI shows symmetrical brain edema at the watershed zones, most common in the parietal and occipital cortical and subcortical areas (Fig. 3). These findings are usually reversible.

Treatment of systemic-onset juvenile idiopathic arthritis includes the use of nonsteroidal anti-inflammatory drugs, oral or intravenous glucocorticoids and biological agents.

Idiopathic recurrent acute pericarditis

The term recurrent pericarditis is used when there is a second episode of acute pericarditis after a period of at least 4 to 6 weeks from an initial episode with no symptoms in between [13]. If the symptoms last more than 3 months, it is then called chronic pericarditis [14].

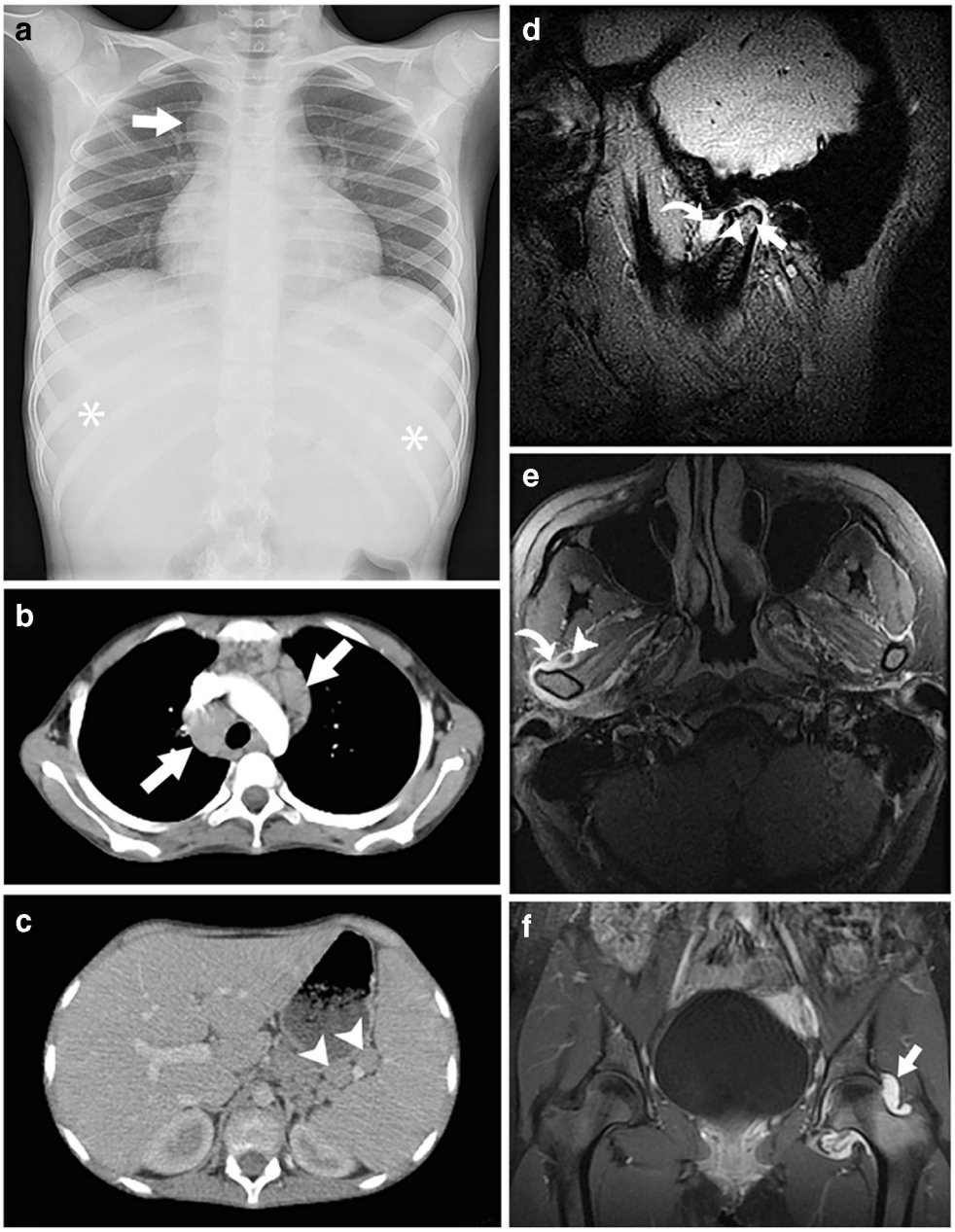

Fig. 1 Systemic-onset juvenile idiopathic arthritis in a 10-year-old girl with daily fever, arthralgias for 1 year and a history of pericarditis. **a** Posteroanterior radiograph of the chest and abdomen shows mediastinal widening (*arrow*) and hepatosplenomegaly (*asterisks*). **b** Axial contrast-enhanced computed tomography (CT) image of the chest confirms multiple enlarged mediastinal lymph nodes (*arrows*). **c** Axial contrast-enhanced CT image of the abdomen shows several enlarged lymph nodes at the splenic hilum (*arrowheads*). **d, e** Four years later, the child presented with deviation of the mandible to the right on the mouth opening. Sagittal T2-weighted gradient echo magnetic resonance imaging (MRI) of the right temporomandibular joint **(d)** shows an erosion in the mandibular condyle (*arrowhead*), bone marrow edema (*arrow*) and intra-articular high signal intensity that may represent joint effusion or synovial thickening (*curved arrow*). Axial contrast-enhanced fat-suppressed T1-weighted MRI of both temporomandibular joints **(e)** shows thickening and enhancement of the synovium on the right, consistent with active synovitis (*curved arrow*) combined with joint effusion (*arrowhead*). **f** Three years later, the child presented with left hip pain. Coronal contrast-enhanced fat-suppressed T1-weighted MRI of the hips shows left proximal femoral bone marrow enhancement and marked synovial thickening and enhancement of the left hip joint (*arrow*)

The most frequent imaging finding is pericardial effusion (Table 1) (Fig. 4). Transthoracic echocardiography is generally the initial diagnostic imaging study performed in these children, but cardiac MRI is better suited to evaluate inflammatory changes. The presence and extent of late gadolinium enhancement of the pericardium are indicators of pericarditis and are useful in guiding the anti-inflammatory treatment [15].

Table 1 Findings in polygenic autoinflammatory diseases

	Systemic-onset juvenile idiopathic arthritis	Idiopathic recurrent pericarditis	Behçet disease	Chronic recurrent multifocal osteomyelitis	Inflammatory bowel disease
Musculoskeletal	Arthritis, classically symmetrical and polyarticular, tenosynovitis		Oligoarthritis, usually asymmetrical and nonerosive of medium and large joints	Multifocal bone lesions, Predilection for the metaphyseal regions of lower extremities and the medial clavicles, association with spondyloarthropathies	Sacroiliitis, avascular necrosis
Cardiopulmonary	Pleural and pericardial effusion	Recurrent pericardial effusion			
Gastrointestinal	Hepatosplenomegaly		Deep penetrating ulcers, particularly in the ileocecal region	Association with inflammatory bowel disease	Bowel wall thickening, sclerosing cholangitis, pancreatitis, cholelithiasis
Neurological	Rare. Intracranial hemorrhage, posterior reversible encephalopathy syndrome		Encephalomyelitis or aseptic meningitis, dural sinus thrombosis		
Vascular disease			Arterial or venous thromboses and aneurysms		
Others	Lymphadenopathy		Ocular involvement	Association with Takayasu arteritis and granulomatosis with polyangiitis	Perianal disease

In contrast to the first episode of acute pericarditis, treatment of idiopathic recurrent acute pericarditis should include a new course of nonsteroidal anti-inflammatory drugs with additional colchicine for 6 months. Anti-tumor necrosis factor-alpha drugs and Interleukin-1 blockade have also been used with good clinical response [16].

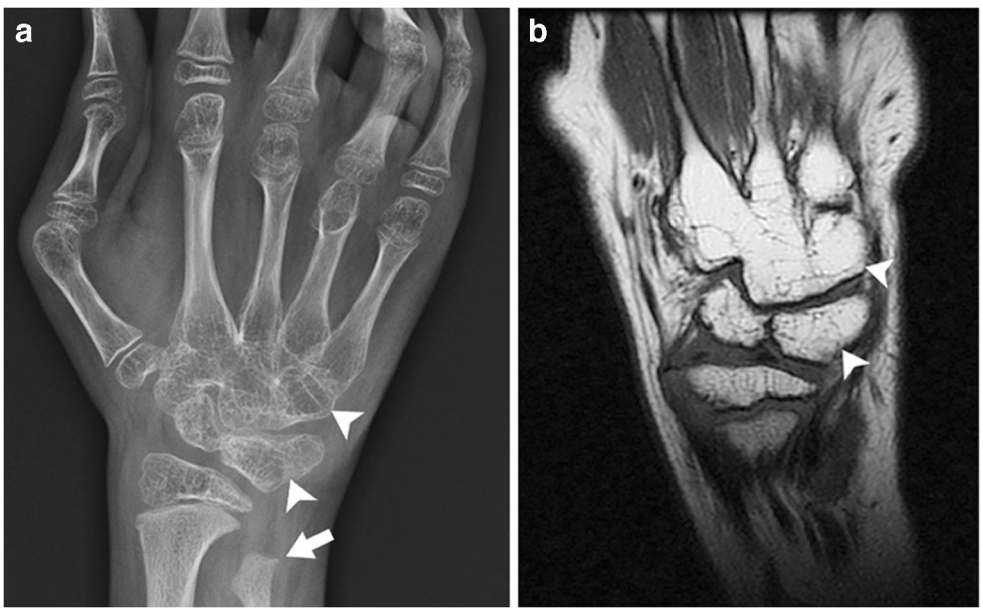

Fig. 2 Systemic-onset juvenile idiopathic arthritis in an 11-year-old boy with left hand pain on flexion. **a**, **b** Anteroposterior radiograph (**a**) and coronal T1-weighted MRI (**b**) of the left hand show carpal and carpometacarpal joint bony ankylosis (*arrowheads*). There is also shortening and deformity of the left ulna (*arrow* in **a**). These are all sequelae of synovitis and erosive changes

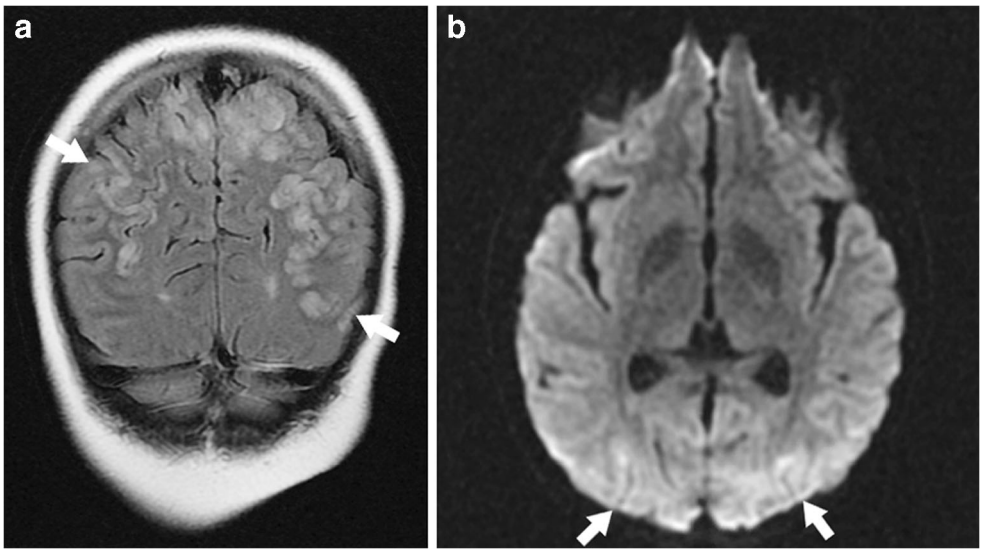

Fig. 3 Systemic-onset juvenile idiopathic arthritis and macrophage activation syndrome in a 10-year-old girl with seizures. **a** Coronal fluid-attenuated inversion recovery (FLAIR) MRI of the brain shows bilateral occipital cortical high signal intensity (*arrows*). **b** Axial diffusion-weighted MRI shows diffusion restriction of the bilateral occipital lesions (*arrows*). These findings are in keeping with posterior reversible encephalopathy syndrome

Behçet disease

Behçet disease is categorized as an inflammatory vascular disease affecting arteries and veins of all kinds and sizes, and is characterized by recurrent oral and genital aphthae, ocular, cutaneous, gastrointestinal, neurological, vascular and/or articular involvement [17].

One of the major characteristic features of Behçet disease is the heterogeneity of the clinical presentation. Imaging findings in Behçet disease are summarized in Table 1. Barium study was traditionally useful in demonstrating the presence of deep, penetrating ulcers, which are characteristic radiographic features of this disease in the gastrointestinal tract. The progression of this penetrating disease may result in multiple complications, including perforation, fistula, hemorrhage and peritonitis [18]. Currently, computed tomography (CT) and MR enterography are used to diagnose Behçet disease, with typical findings including bowel wall thickening and enhancement associated with deep penetrating ulcers, particularly in the ileocecal region. Polypoid appearance of the intestinal surface and homogeneous enhancement of the small-bowel wall are more common in children with Behçet disease than in patients with Crohn disease [19]. A layered or stratified enhancement pattern, the presence of strictures, and the involvement of a long segment and, particularly, of more proximal ileal segments favor Crohn disease [19]. However, in the absence of extraintestinal manifestations, it may be impossible to differentiate intestinal Behçet disease from Crohn disease. On occasion, Behçet disease can manifest as a cecal mass or an aneurysmal dilatation of the terminal ileum mimicking a malignant tumor, particularly lymphoma [20–22].

Cardiopulmonary and renal involvement is rare in children. Neurological manifestations may include encephalomyelitis or aseptic meningitis (Fig. 5), as well as dural sinus thrombosis (Fig. 6). Oligoarthritis is common, usually asymmetrical and nonerosive and most frequently affects medium and large

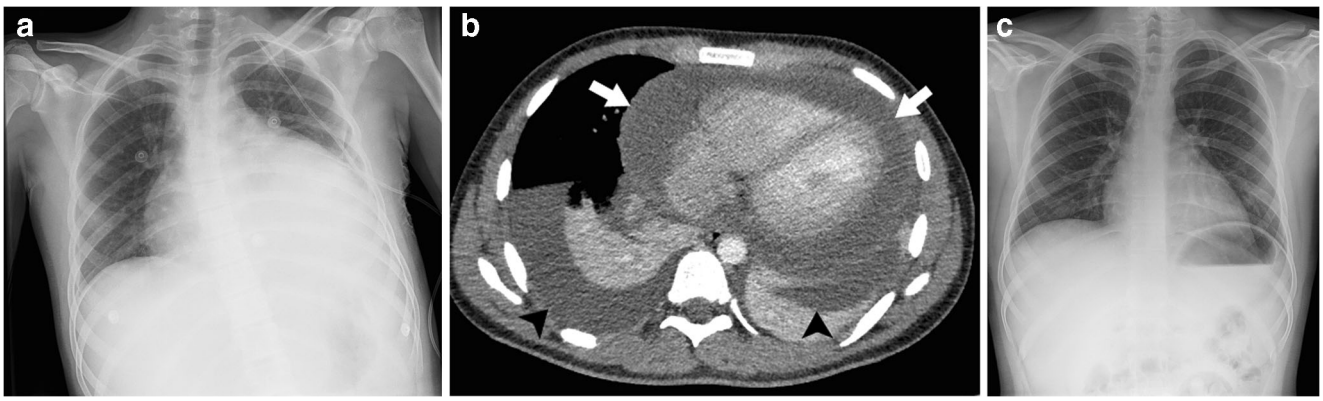

Fig. 4 Acute recurrent pericarditis in a 15-year-old boy with recurrent episodes of asthenia, fever and dyspnea. **a** Anteroposterior radiograph of the chest shows enlargement of the cardiac silhouette. **b** Axial contrast-enhanced CT image of the chest shows a large pericardial effusion (*arrows*) and bilateral pleural effusions (*arrowheads*). **c** Posteroanterior radiograph of the chest after treatment shows normal cardiac silhouette

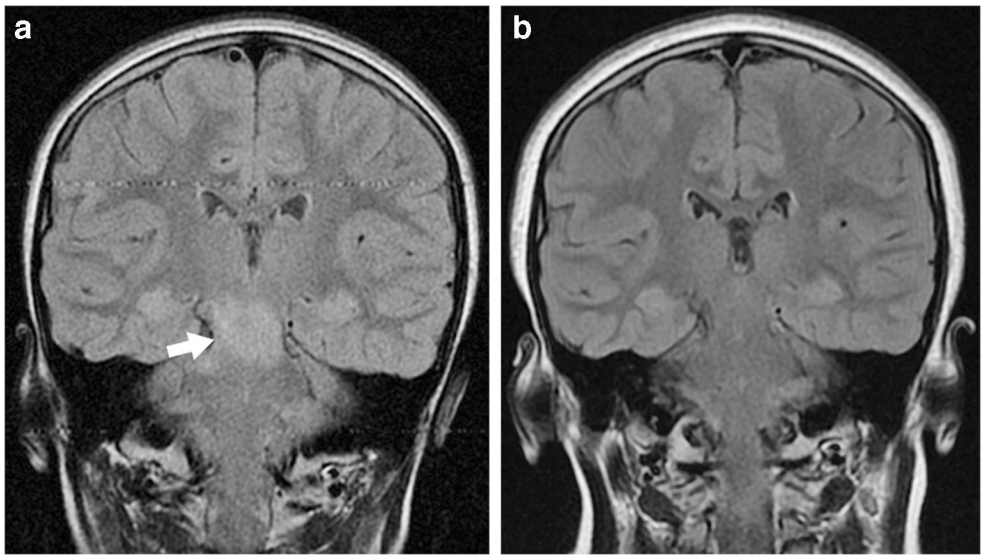

Fig. 5 Behçet disease in a 10-year-old girl with recurrent fever and meningoencephalitis. **a** Coronal fluid-attenuated inversion recovery (FLAIR) MRI of the brain at presentation shows high signal intensity in the midbrain, extending into the cerebral peduncles and pons (*arrow*). There was associated leptomeningeal enhancement and central punctate enhancement at the right cerebral peduncle (not shown). **b** Coronal FLAIR MRI of the brain at the 7-month follow-up shows a normal appearance with resolution of the previous findings

joints including the knees, ankles, wrists and elbows. Myositis is uncommon. The vasculitis of Behçet disease is characterized by venous thrombosis and arterial occlusions or aneurysms [23, 24]. Thrombosis of the hepatic veins can result in Budd-Chiari syndrome [23, 24].

Treatment of Behçet disease is variable, depending on the location and severity of involvement. Topical treatment with sucralfate suspension or corticosteroids is used initially for ulcers [23]. Prednisone is frequently the first treatment option for multiple manifestations. Azathioprine and biologics, mainly tumor necrosis factor-alpha blocking agents, are useful for uveitis. Low-dose methotrexate, azathioprine, anti-tumor necrosis factor agents and cyclophosphamide are helpful for central nervous system disease [23].

Chronic recurrent multifocal osteomyelitis

Chronic recurrent multifocal osteomyelitis, also named chronic nonbacterial osteomyelitis, is a rare type of skeletal inflammation that occurs mainly in children and adolescents, affects females more frequently and shows a worldwide distribution.

Chronic recurrent multifocal osteomyelitis remains a diagnosis of exclusion, as no specific diagnostic test is available [25]. Infectious osteomyelitis and neoplasms such as osteosarcoma, Ewing sarcoma, lymphoma, neuroblastoma, leukemia, Langerhans cell histiocytosis, osteoid osteoma and osteoblastoma are often part of the differential diagnosis (Table 2) [4, 25–38]. Multiple bone lesions, a relapsing-remittent course, involvement of locations not typical for infectious osteomyelitis, such as the clavicle, imaging findings

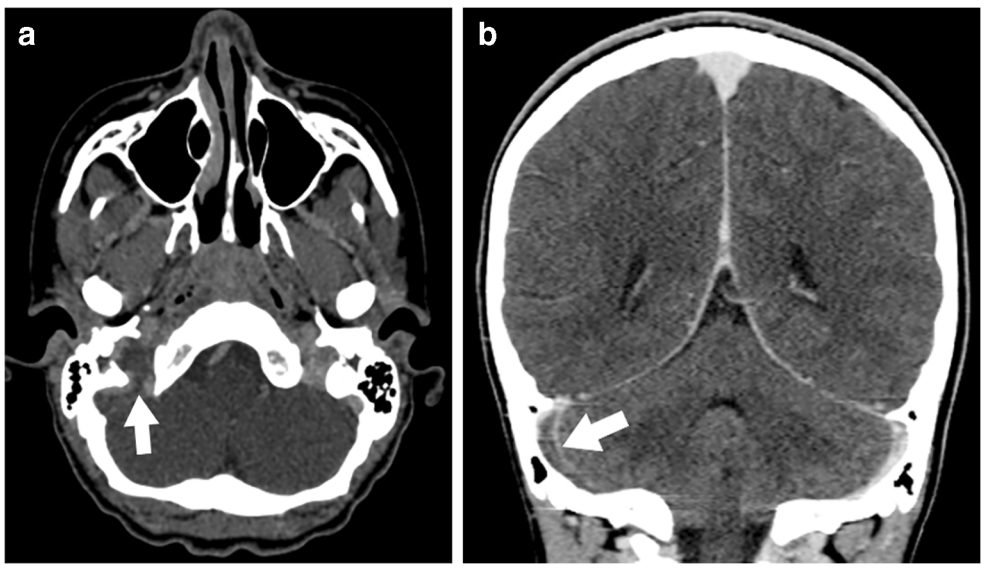

Fig. 6 Behçet disease in a 12-year-old boy with constitutional symptoms and diplopia. Axial (**a**) and coronal (**b**) contrast-enhanced CT images of the brain show a tubular filling defect in the right sigmoid sinus consistent with venous sinus thrombosis (*arrows*)

Table 2 Imaging differential diagnosis of chronic recurrent multifocal osteomyelitis

Entity		Imaging findings
Chronic recurrent multifocal osteomyelitis		Common locations: pelvis, lower extremities, clavicle, shoulders, spine Frequent involvement of the physis in tubular bones, multifocality and bilateral symmetry Radiographic findings: lytic metaphyseal lesion with sclerotic rim and progression of sclerosis with time MRI findings: bone marrow edema with variable soft-tissue edema, less apparent in the axial skeleton Elevated apparent diffusion coefficient values on diffusion-weighted imaging
Juvenile idiopathic arthritis		Acute inflammatory findings: soft-tissue swelling, joint effusion, synovial thickening and enhancement, tenosynovitis, enthesopathy, bone marrow edema Chronic inflammatory findings: bone erosions, joint space narrowing, bone ankylosis, growth disturbances and joint malalignment
Infectious osteomyelitis		Usually one bone affected Involvement of metaphysis and metaphyseal equivalent Radiographic findings: regional osteopenia, periosteal reaction (variable; may appear aggressive), focal bony lysis MRI findings: low signal intensity of the central component on T1-weighted images and high signal intensity on STIR, with surrounding bone marrow edema Presence of abscess, fistula or sequestrum
Benign osseous tumors	Osteoid osteoma	Radiographic findings: intracortical nidus, with or without internal mineralization, accompanied by cortical thickening and reactive sclerosis in a long bone shaft MRI findings: low to intermediate signal intensity of the nidus on T1-weighted images and variable signal intensity on T2-weighted images, with adjacent bone marrow and soft-tissue edema, and joint effusion if intra-articular in location Dynamic contrast-enhanced MRI findings: early arterial peak enhancement is useful to differentiate osteoid osteoma from osteomyelitis (Brodie abscess), which shows slow enhancement with no arterial peak, and also to diagnose recurrence after percutaneous treatment, as after successful treatment there is no enhancement or only delayed gradual enhancement
	Osteoblastoma	Tends to affect the axial skeleton more often than osteoid osteoma Radiographic findings: Usually more expansile than osteoid osteoma, larger than 2 cm, and with less reactive surrounding sclerosis MRI findings: hypo- to isointense on T1-weighted images and iso- to hypointense on T2-weighted images with avid contrast enhancement, foci of decreased intensity due to calcifications, and surrounding bone marrow and soft-tissue edema
Malignancy	Ewing sarcoma	Radiographic findings: Moth-eaten/permeative destructive lesion in the diaphysis of long bones with large soft-tissue mass and aggressive periosteal reaction. Frequent osseous metastases making lesion polyostotic MRI findings: marrow replacement and cortical destruction with an associated circumferential but asymmetrical soft-tissue mass with homogeneous and intermediate signal intensity on T1-weighted images, and low to intermediate signal intensity on T2-weighted images. High signal intensity areas on T2-weighted images may be seen in large lesions due to hemorrhage or necrosis
	Osteosarcoma	Intramedullary mass with immature cloud-like bone formation in the metaphyses of long bones Often large at the time of diagnosis There may be osseous metastases MRI findings: intramedullary mass with intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted images. Areas of low signal intensity on T1- and T2-weighted images due to mineralized matrix, foci of hemorrhage with high signal intensity on T1- and T2-weighted images, and necrosis with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images are common
	Lymphoma	Primary pediatric lymphoma of bone: • Often multifocal at presentation • Nonspecific features although most commonly permeative lytic pattern • Typically affects the diaphysis or metadiaphysis of long bones or the flat bones of the axial skeleton. Secondary bone involvement from disseminated lymphoma: • Mixed lytic-sclerotic pattern is more common • Tends to favor the axial skeleton • Nodal disease present MRI findings: bone marrow involvement of low signal intensity on T1-weighted images, high signal intensity on T2-weighted images, and contrast enhancement
	Leukemia	Radiographic findings: osteopenia (most common), radiolucent metaphyseal bands, periosteal reaction and coarse trabeculation MRI findings: bone marrow infiltration with decreased signal intensity on T1-weighted images, increased signal intensity on T2-weighted images, and usually diffuse enhancement with contrast

Table 2 (continued)

Entity	Imaging findings	
	Neuroblastoma	Radiographic findings: osteolytic focus with or without periosteal reaction, or lucent horizontal metaphyseal line, vertebral collapse with spinal metastases, and widening of the cranial sutures secondary to dural metastases MRI findings: bone metastases are hypointense on T1-weighted images, hyperintense on T2-weighted images, and intense enhancement with contrast
	Langerhans cell histiocytosis	Radiographic findings: Skull: "punched-out" lesion, beveled edge (asymmetrical destruction of inner and outer tables), geographical skull (lesions grow, coalesce, and become map-like) Spine: vertebra plana (most common cause of vertebra plana in children, usually in thoracic spine) Long bones: more commonly involved in children, diaphyseal or metaphyseal region Flat bones: "floating teeth" if enough alveolar destruction, lytic lesion with sclerotic rim and surrounding areas of sclerosis more common in iliac bone MRI findings: soft-tissue component is hyperintense on T2-weighted images and isointense on T1-weighted images, with enhancement with contrast

in keeping with subacute or chronic osteomyelitis but with no abscess, fistula or sequestrum, absence of an infectious microorganism and improvement with nonsteroidal anti-inflammatory drugs but not antibiotics suggest the diagnosis [25, 39, 40]. In addition, chronic recurrent multifocal osteomyelitis may be associated with other inflammatory disorders of the skin, such as pustulosis palmoplantaris or acne, as well as gastrointestinal tract diseases, including inflammatory bowel disease, and vasculitis such as Takayasu arteritis and granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) [25].

Chronic recurrent multifocal osteomyelitis is usually bilateral and multifocal at presentation but often lacks clinical and temporal symmetry [25]. Typical imaging findings (Table 1) consist of lytic and sclerotic metaphyseal lesions in the long bones, especially involving the lower extremities and the medial aspect of the clavicles (Fig. 7) [39]. In fact, involvement of the clavicles is one of the distinctive features of chronic recurrent multifocal osteomyelitis, which is a rare location for hematogenous osteomyelitis. In addition, excluding neoplastic processes, chronic recurrent multifocal osteomyelitis is the most frequent disease affecting the clavicle in children and young adults, as well as the most frequent pathology involving the medial third of the clavicle at any age [25]. As opposed to synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome, clavicular disease in chronic recurrent multifocal osteomyelitis is not associated with the sternoclavicular joint. In addition to the clavicle and long bones, involvement of the vertebral bodies, pelvis, ribs, and mandible is also common [25].

At presentation, radiographs may be completely normal or show only osteopenia, however, MRI may show bone marrow edema at this stage. With time, radiographs typically show a metaphyseal osteolytic lesion abutting the growth plate demarcated by a thin sclerotic rim (Fig. 8) [41]. With disease progression, sclerosis gradually increases around the lytic lesion and therefore chronic lesions usually become mainly sclerotic with associated hyperostosis [25]. Lesions also occur in nontubular bones, in metaphyseal-equivalent regions adjacent to cartilage.

MRI may suggest the diagnosis and show the typical periphyseal, multifocal pattern [42]. It can also detect clinically occult involvement and show the extension of the bone and soft-tissue lesions (Fig. 9). Whole-body MRI with short tau inversion recovery (STIR) images is the imaging technique of choice used at our institution as it allows identification of asymptomatic

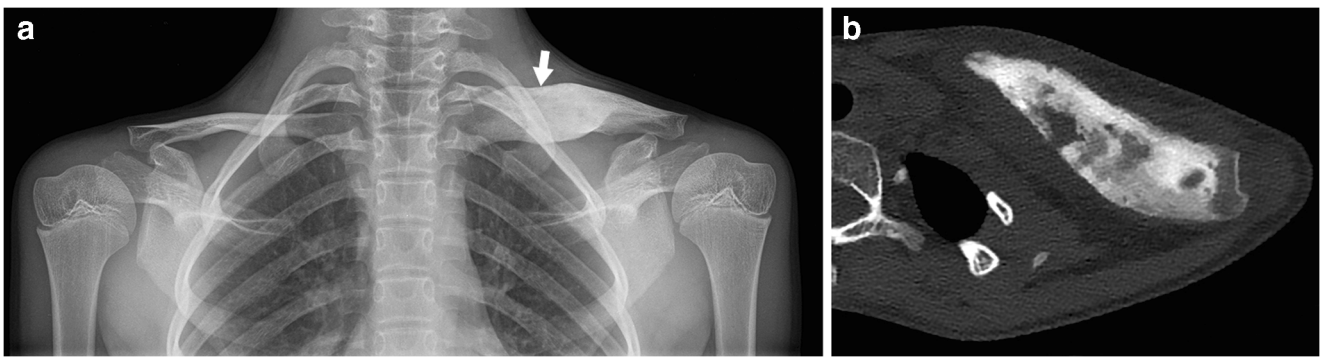

Fig. 7 Chronic recurrent multifocal osteomyelitis in a 15-year-old girl with left shoulder pain. **a** Posteroanterior radiograph of the upper chest shows enlargement and sclerosis of the medial aspect of the left clavicle (*arrow*), a common site of involvement in chronic recurrent multifocal osteomyelitis. **b** Axial CT image shows thickening of the left clavicle with a mixed pattern of lysis and sclerosis

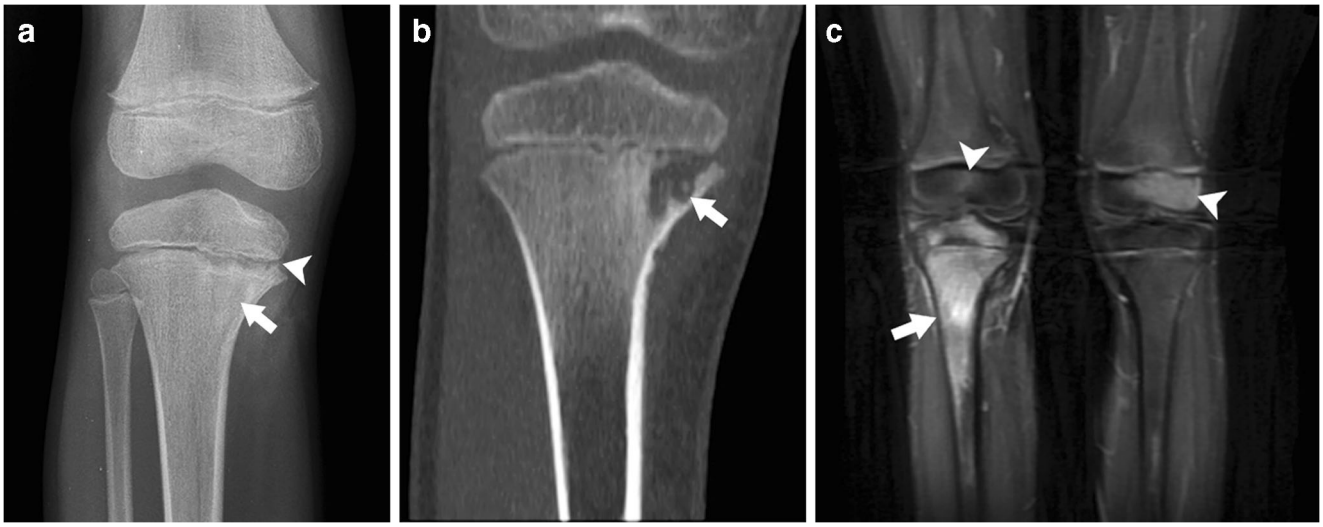

Fig. 8 Chronic recurrent multifocal osteomyelitis in a 15-year-old boy with polyarticular pain that is more prominent in the right knee. **a** Anteroposterior radiograph of the right knee shows widening and irregularity of the medial aspect of the proximal tibial physis (*arrowhead*) and an ill-defined lesion in the adjacent metaphysis (*arrow*). **b** Coronal reformatted CT image of the right proximal tibia shows a focal lytic lesion at the medial aspect of the proximal metaphysis (*arrow*). **c** Coronal short tau inversion recovery (STIR) MRI of the knees shows increased signal intensity involving the proximal epiphysis, metaphysis and diaphysis of the right tibia (*arrow*), as well as the distal epiphysis of both femurs (*arrowheads*), more extensive on the left

lesions and establishes a baseline of disease burden [43]. The protocol includes coronal images of the whole body and sagittal images of the spine. Whole-body imaging can also be done with Technetium-99 bone scintigraphy, which shows areas of increased uptake. However, MRI is preferred because of the lack of radiation and the better assessment of the anatomy and soft tissues [44]. Furthermore, the physiological uptake of the physis seen on the bone scan can be misleading. Positron emission tomography has been used clinically to detect chronic osteomyelitis, but its use in chronic recurrent multifocal osteomyelitis has not been described [45]. In addition to the typical metaphyseal involvement, accompanying epiphyseal lesions are also frequent [42]. Recognizing transphyseal involvement and secondary physeal bars is important as it allows identifying children at higher risk for growth deformities [25]. Diaphyseal involvement is rare, although it usually occurs next to the affected metaphyses [46]. MRI may show periostitis, inflammatory changes in the adjacent soft tissues, involvement of the physis and articular inflammation with synovitis, joint effusion and destructive changes within the joint cartilage and subchondral bone [25]. Active lesions typically show increased signal intensity on STIR and fat-suppressed T2-weighted images, decreased signal intensity on T1-weighted images, and increased apparent diffusion coefficient values on diffusion-weighted imaging [47]. MRI is also useful for follow-up, particularly when there is suspicion for inflammatory activity in children with marked sclerosis or hyperostosis. In these patients, areas of sclerosis with no superimposed inflammation appear hypointense on T1- and T2-weighted images [25]. Findings such as abscess, fistula or sequestrum are more characteristic of infectious osteomyelitis rather than chronic recurrent multifocal osteomyelitis.

Nonsteroidal anti-inflammatory drugs represent the initial treatment option. Second-line treatment agents include corticosteroids, azathioprine, disease-modifying antirheumatic drugs, bisphosphonates, biologics, mainly tumor necrosis factor-alpha and Interleukin-1 blocking agents, and other immune modulators [41].

Inflammatory bowel disease

Inflammatory bowel disease is a chronic, relapsing autoinflammatory disease of the gastrointestinal tract, and is often categorized in three subtypes: Crohn disease, ulcerative colitis and unclassified [48]. Inflammatory bowel disease has a prevalence of 1 in 1,000 inhabitants in Western countries [48]. Approximately 25% of inflammatory bowel disease occurs in children [49], in whom Crohn disease tends to be more common than ulcerative colitis, especially in males [48].

Symptoms at presentation in children are diverse and include abdominal pain, diarrhea (with or without bloody stools), perianal lesions, growth retardation and weight loss [48]. Extraintestinal manifestations may be seen, including hepatobiliary, pancreatic, genitourinary, musculoskeletal, pulmonary, cardiac, ocular and dermatological symptoms.

Ulcerative colitis and Crohn disease have distinctive characteristics that help to establish a specific diagnosis. Crohn disease can involve the gastrointestinal tract from mouth to anus with multiple inflammatory lesions separated by normal bowel segments. In addition, these lesions may involve the entire bowel wall from the mucosa to serosa causing deep ulcerations and local complications, such as abscesses and

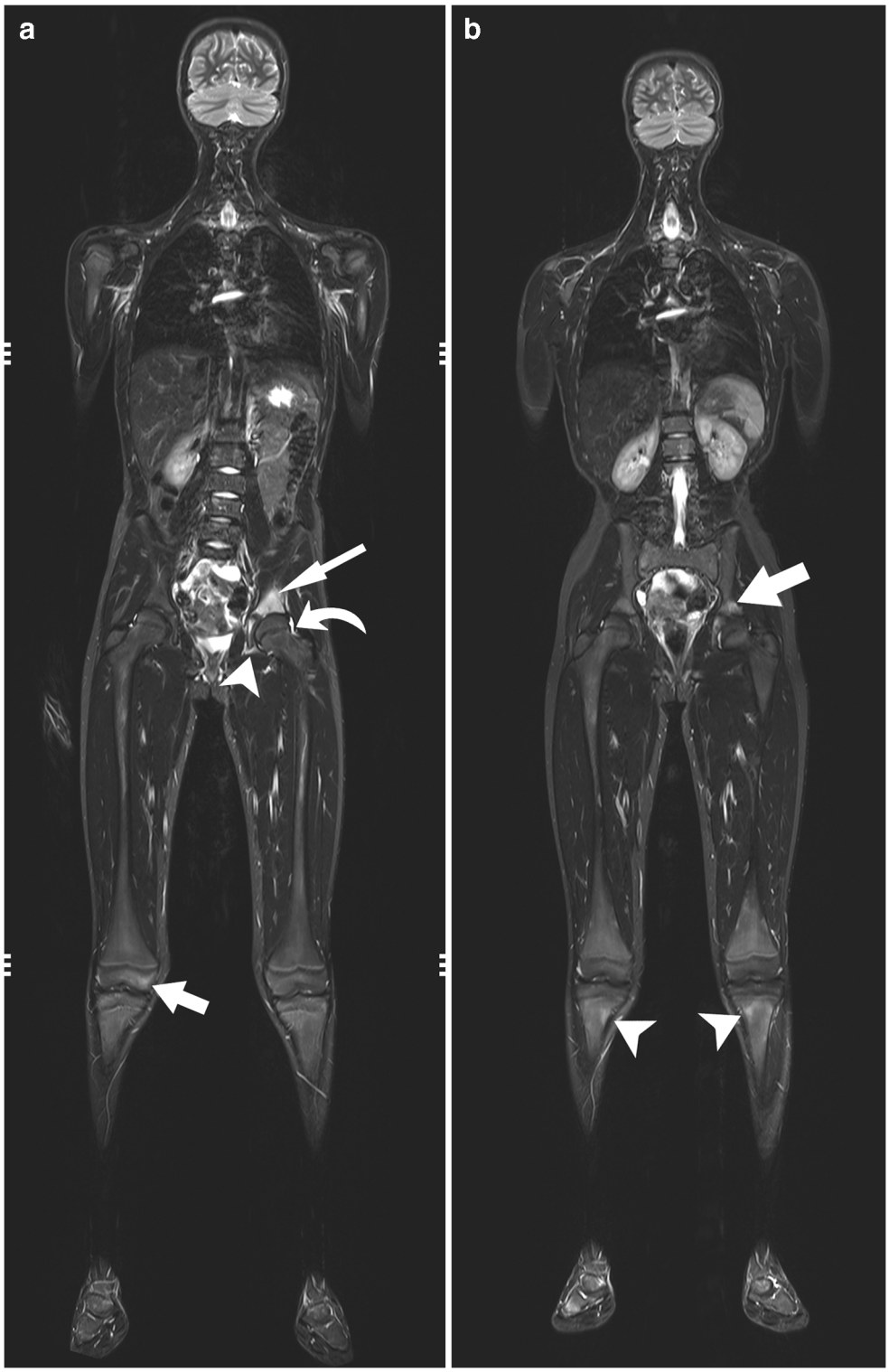

Fig. 9 Chronic recurrent multifocal osteomyelitis in an 11-year-old girl with a 3-week history of persistent left hip pain, daily fevers and weight loss. **a** Coronal STIR whole-body MRI at presentation shows hyperintense foci in the left acetabulum and adjacent iliac bone (*long arrow*) and ischium, adjacent soft tissues (*arrowhead*) and right medial femoral condyle (*short arrow*). There is also a small left-side hip joint effusion (*curved arrow*). **b** Coronal STIR whole-body MRI 4 months later shows significant improvement in the signal abnormality within the left acetabulum and ischium (*arrow*) and resolution of the signal abnormality within the right distal femoral epiphysis. New bone marrow hyperintense foci are seen in the bilateral proximal tibial metaphyses (*arrowheads*)

fistulas [48]. Bowel strictures are also relatively frequent in Crohn disease. In contrast, in ulcerative colitis, lesions are limited to the mucosa and to the large bowel, and perianal lesions are uncommon and limited [48]. Unclassified inflammatory bowel disease refers to colitis with equivocal features for Crohn disease or ulcerative colitis.

The diagnosis of inflammatory bowel disease requires correlation of clinical, biological, endoscopic, histological and imaging findings [48] as shown in the revised Porto criteria proposed by the European Society for Paediatric Gastroenterology Hepatology and Nutrition [50, 51] and exclusion of potential mimickers (Table 3) [19, 52–58]. US

and MRI are the imaging techniques most frequently used to diagnose and manage inflammatory bowel disease in children, although radiography, fluoroscopic studies and CT may also be useful [59]. The imaging findings in inflammatory bowel disease are summarized in Table 1. Transabdominal US may detect bowel inflammation and evaluate the severity and extent of the disease although its value is limited for the small bowel compared to MR enterography. Increased bowel wall thickness (>3 mm) is the main sonographic finding (Fig. 10) [60]. Other sonographic findings include hyperemia, abnormal bowel wall echogenicity, abnormal bowel margin, increased echogenicity of the surrounding fat and lymphadenopathy [50]. US may also depict complications such as inflammatory mass (phlegmon/abscess), stricture, sinus tract and fistula. MR enterography and CT have similar indications and diagnostic performance, but MR enterography is preferred in children due to the lack of ionizing radiation [50, 60]. MRI of the bowel needs fast acquisition techniques and luminal distension [61]. The main MRI findings are mural enhancement, wall thickening, intramural edema (T2 hyperintensity), ulcerations, sacculations, stricture, fistula, sinus tract, inflammatory phlegmon, abscess (fluid collection with enhancing rim with or without air, with diffusion restriction),

Table 3 Differential diagnosis of inflammatory bowel disease

Entity	Etiology/additional information	Imaging findings
Infection	Bacterial enterocolitis	Mesenteric lymphadenopathy Wall thickening of the colon and/or ileum Decreased small bowel motility
	Viral gastroenteritis	Mesenteric lymphadenopathy Bowel wall thickening is rare
	Tuberculous enteritis and colitis	Concentric heterogeneous/hypoechoic bowel wall thickening, particularly at the ileocecal region Hypoechoic lymphadenopathy Ascites Fluid collections
Pseudomembranous colitis	Antibiotic-associated diarrhea	Marked hypoechoic/heterogeneous thickening of the colonic wall Increased echogenicity of pericecal fat
Neutropenic colitis (typhlitis)	Most commonly occurs in immunocompromised patients, chemotherapy and steroid therapy patients	Marked bowel wall thickening involving particularly the terminal ileum, cecum, and ascending colon
Primary immunodeficiencies	Chronic granulomatous disease, common variable immune deficiency, agammaglobulinemia, Hyper-IgM, Hyper-IgE, and severe combined immunodeficiency	Chronic granulomatous disease: Esophageal stricture Circumferential wall thickening at the antrum causing gastric outlet obstruction Duodenal fold thickening Enteric fistulas or sinus tracts Lymphadenopathy
Eosinophil-associated diseases	Concomitant allergic disorders, including asthma, rhinitis, eczema and drug or food intolerances and family history of atopic diseases are common	Skipped segments of bowel wall thickening "Halo" sign: layered appearance of the bowel wall secondary to submucosal edema "Araneid limb-like" sign: spider leg appearance due to diffuse mucosal thickening and enhancement in the mucosal sinuses Eosinophilic esophagitis: "ringed esophagus" or smooth long segment narrowing Ascites
Vasculitis	Henoch-Schönlein purpura	Multifocal symmetrical, circumferential bowel wall thickening with target appearance on contrast-enhanced CT Free intraperitoneal fluid Ileus of affected loop Vascular engorgement in adjacent mesentery Lymphadenopathy
Lymphoma	Non-Hodgkin lymphoma (most common malignancy of the gastrointestinal tract in children)	Mass commonly involving the ileocecal region that may present with intussusception or intestinal obstruction
Behçet syndrome	Common findings: oral and genital aphthae, ocular, and/or articular involvement	Bowel wall thickening and enhancement with deep penetrating ulcers, particularly in the ileocecal region, and polypoid appearance of the intestinal surface

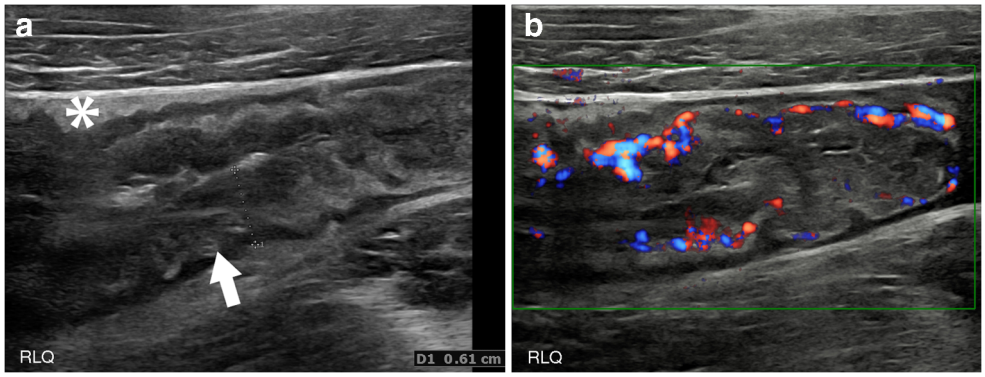

Fig. 10 Crohn disease in a 16-year-old boy with symptoms of small bowel obstruction. **a** Transverse sonogram of the right lower quadrant of the abdomen shows marked wall thickening of the terminal ileum (*arrow*), measuring 0.61 cm, with increased echogenicity of the adjacent fat (*asterisk*). **b** Transverse sonogram with color Doppler interrogation shows marked hyperemia of the thickened bowel wall, which is considered a sign of disease activity

perienteric edema/engorged vasa recta (comb sign), and mesenteric venous thrombosis [60] (Fig. 11). Diminished peristalsis may also be present in small bowel Crohn disease [62]. Extraintestinal findings such as sacroiliitis, sclerosing cholangitis, avascular necrosis, pancreatitis, nephrolithiasis, cholelithiasis and perianal disease can also be depicted.

The current goals of treatment in inflammatory bowel disease are to eliminate symptoms and restore quality of life, restore normal growth and eliminate complications. Corticosteroids, enteral nutrition therapy, aminosalicylates, immunomodulators, anti-tumor necrosis factor therapy and surgery are the main therapeutic options [63].

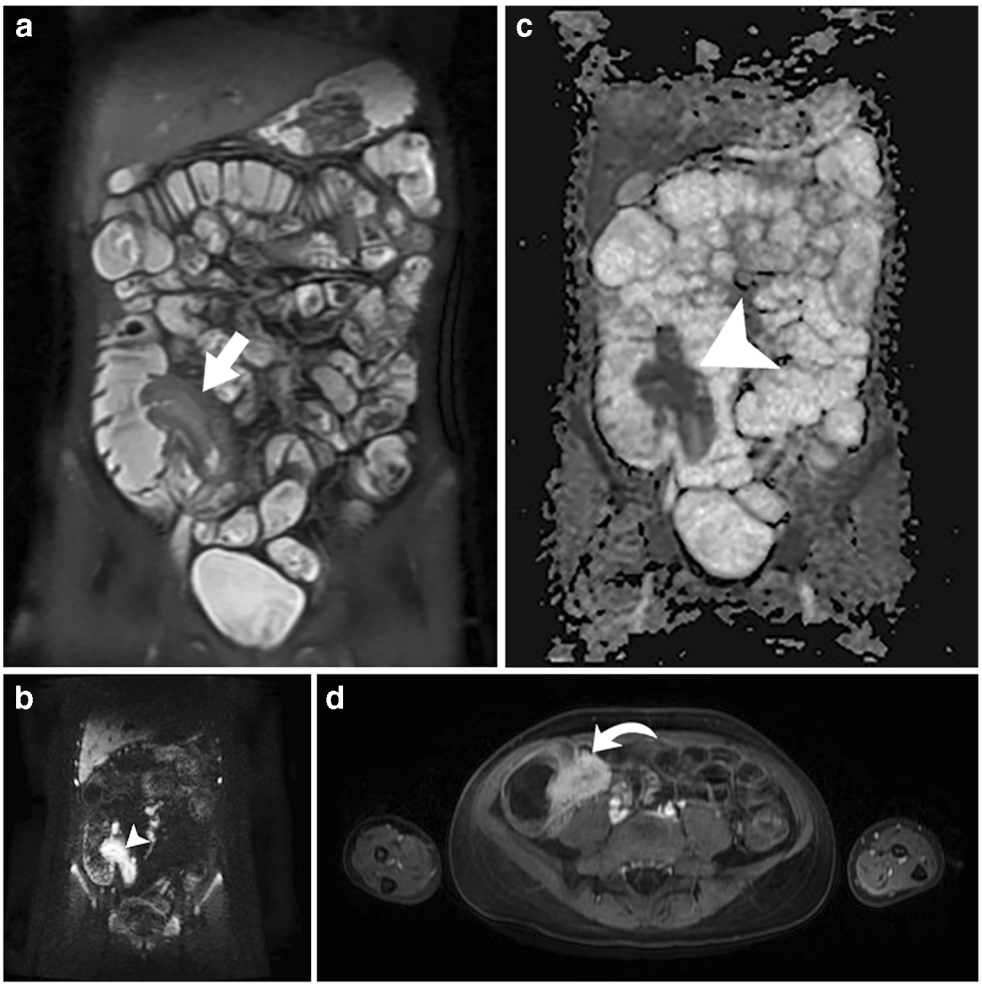

Fig. 11 Crohn disease in a 9-year-old girl with abdominal pain and diarrhea. **a** Coronal fat-suppressed T2-weighted image shows marked wall thickening and edema of the terminal ileum (*arrow*). **b** Coronal diffusion-weighted MRI (b=800 s/mm^2) shows thickening and increased signal intensity of the terminal ileum (*arrowhead*). **c** Coronal apparent diffusion coefficient map MRI shows the corresponding hypointensity of the terminal ileum consistent with marked diffusion restriction (*arrowhead*). **d** Axial fat-suppressed contrast-enhanced T1-weighted MRI shows increased enhancement of the thickened terminal ileum (*curved arrow*) denoting inflammation

Conclusion

Autoinflammatory diseases include a broad spectrum of disorders with a wide variety and, often, nonspecific presentations. Imaging provides clues for diagnosis and is useful to assess organ involvement and disease extent. Systemic-onset juvenile idiopathic arthritis is associated with arthritis, lymphadenopathy, hepatosplenomegaly and serositis. Idiopathic recurrent pericarditis is characterized by recurrent pericardial effusions. Behçet disease is characterized by deep penetrating ulcers, particularly in the ileocecal region, neurological vascular and articular involvement. Multiple bone lesions with predilection for the metaphyses of the lower extremities and the medial clavicles are typical of chronic recurrent multifocal osteomyelitis. Bowel wall thickening is the main finding in inflammatory bowel disease, although abdominal complications and extraintestinal findings may be detected on imaging.

Compliance with ethical standards

Conflicts of interest None

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