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The utility of ultrasound in juvenile idiopathic arthritis

Przydatność ultrasonografii w diagnostyce młodzieńczego idiopatycznego zapalenia stawów

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Abstract

Juvenile idiopathic arthritis is a heterogeneous group of idiopathic inflammatory arthropathies affecting children younger than 16 years of age and persisting for six weeks or longer. Introduction of novel biological medications has dramatically changed the prognosis of juvenile idiopathic arthritis. Their ability to inhibit the main mechanisms responsible for persistent inflammation prevents joint damage and chronic joint dysfunction. Achieving this is only possible with a prompt diagnosis and treatment. Ultrasonography is one of the main imaging methods used in the diagnosis of juvenile idiopathic arthritis. In this article, we review the latest literature on ultrasound imaging in juvenile idiopathic arthritis. Musculoskeletal ultrasound is a constantly developing imaging technique and becomes an even more useful adjunct in clinical practice. For juvenile idiopathic arthritis, it enables evaluation of a number of peripheral joints and identification of features of active arthritis, such as synovitis, tenosynovitis, enthesitis, and destructive lesions, such as erosions, subchondral and subcortical cysts, and cartilage loss. Musculoskeletal ultrasound is used for the early diagnosis, treatment monitoring and identification of disease remission or its complications. Contrary to other imaging methods, it is widely available and safe (no exposure to radiation). It does not require the patient to be motionless, and can be performed in a dynamic way, providing additional information on e.g. tendon sliding. Furthermore, a number of procedures can be performed under ultrasound guidance.

Keywords: juvenile idiopathic arthritis, ultrasound, juvenile spondyloarthritis, musculoskeletal system

Streszczenie

Młodzieńcze idiopatyczne zapalenie stawów stanowi niejednorodną grupę idiopatycznych artropatii zapalnych występujących u dzieci poniżej 16. roku życia i trwających przynajmniej sześć tygodni. Wprowadzenie nowych leków biologicznych radykalnie zmieniło rokowanie w tej chorobie. Ich zdolność do hamowania głównych mechanizmów odpowiedzialnych za przewlekłe stany zapalne zapobiega uszkodzeniom oraz przewlekłej dysfunkcji stawów. Jest to możliwe tylko dzięki szybkiemu rozpoznaniu i wczesnemu wprowadzeniu leczenia. Jedną z głównych metod obrazowania stosowanych w diagnostyce młodzieńczego idiopatycznego zapalenia stawów jest badanie ultrasonograficzne. Niniejszy artykuł stanowi przegląd najnowszej literatury dotyczącej obrazowania ultrasonograficznego w młodzieńczym idiopatycznym zapaleniu stawów. Ultrasonografia układu mięśniowo-szkieletowego to ciągle rozwijająca się technika obrazowania, która staje się coraz bardziej przydatna w praktyce klinicznej. W przypadku młodzieńczego idiopatycznego zapalenia stawów umożliwia ocenę wielu stawów obwodowych oraz rozpoznanie cech aktywnego zapalenia stawów, takich jak zapalenie błony maziowej, zapalenie pochewki ścięgna, entezopatie i zmiany destrukcyjne: nadżerki, torbiele podchrzęstne i podkorowe, utrata chrząstki. Ultrasonografię układu mięśniowo-szkieletowego wykorzystuje się do wczesnej diagnozy, monitorowania leczenia i rozpoznawania remisji choroby lub jej powikłań. W przeciwieństwie do innych metod obrazowania technika ta jest powszechnie dostępna, bezpieczna (brak promieniowania), nie wymaga od pacjenta unieruchomienia, może być wykonywana w sposób dynamiczny, dostarczając dodatkowych informacji, np. dotyczących ślizgania ścięgna, pozwala na realizowanie wielu procedur pod jej kontrolą.

Słowa kluczowe: młodzieńcze idiopatyczne zapalenie stawów, badanie ultrasonograficzne, młodzieńcze spondyloartropatie, układ mięśniowo-szkieletowy

INTRODUCTION

Articular pain and joint swelling in children are common reasons for consulting a general practitioner. A broad spectrum of conditions can trigger joint pain or swelling. They vary from simple injuries like a sprained ankle to very rare and life-threatening disorders like bone tumours. If articular pain or swelling persists, a physician should consider further diagnosis to exclude any underlying diseases.

Juvenile idiopathic arthritis (JIA) is one of the most common reasons for chronic joint pain in children. The disease mainly involves peripheral skeleton, with the knee being the most frequently affected joint⁽¹⁾. JIA is a heterogeneous group of idiopathic inflammatory arthropathies affecting children younger than 16 years of age and persisting for six weeks or longer⁽²⁾. It is the most common rheumatic disease reported in children⁽³⁾, and significantly contributes to disability among children⁽⁴⁾. Western population studies of JIA have reported an incidence ranging from 2 to 20 per 100,000 inhabitants and prevalence of 16 to 150 per 100,000 inhabitants⁽⁵⁾. The aetiology of chronic arthritis in JIA still remains unclear. However, several factors such as vaccinations, infections, the presence of specific human leukocyte antigen (HLA) alleles, such as HLA-A2, are taken into consideration^(1,4).

JIA is a group of diseases that share a specific characteristic: a prolonged synovial inflammation that can lead to damage of cartilage and bone. This can severely compromise the function of an affected joint and, consequently, the quality of patient's life⁽⁶⁾.

Introduction of novel biological medications has dramatically changed the prognosis of JIA. Their ability to inhibit

the main mechanisms responsible for persistent inflammation prevents joint damage and dysfunction. Achieving this is only possible with a prompt diagnosis and treatment⁽⁵⁾.

CLASSIFICATION OF JIA

There are seven subtypes of JIA according to the International League of Associations for Rheumatology (ILAR) JIA classification (Tab. 1). The diagnosis is based on the clinical picture and laboratory findings. Oligoarthritis, which affects 27–60% of children with JIA, is the most frequent subtype. It is the most common subtype in western developed countries, whereas the polyarthritis subtype predominates in India and South Africa. Oligoarthritis most often involves the knee, followed by the ankle⁽⁷⁾. Psoriatic arthritis, enthesitis-related arthritis (ERA) and undifferentiated arthritis are seronegative subtypes of JIA and can be also classified as juvenile spondyloarthritis (JSpA). Enthesitis, oligoarthritis of lower extremities, axial involvement as well as the presence of HLA-B27 are key features of JSpA^(1,2).

ULTRASOUND EXAMINATION IN JIA

JIA is a clinical diagnosis and medical imaging plays a crucial role in supporting the diagnosis. It is also used in monitoring therapeutic response as well as for detection of chronic changes⁽⁴⁾.

Classical radiography is the standard examination in the assessment of JIA, especially in the differential diagnosis and treatment monitoring⁽⁸⁾. Although this modality is useful in detecting advanced destructive lesions, it is not able to visualise early signs of inflammatory changes in soft tissues, such as synovitis, enthesitis, tenosynovitis, or bursitis.

Category	Clinical presentation and laboratory markers
Systemic arthritis	4–20% of children with JIA. One or more joints are affected along with or preceded by at least two weeks of fever occurring daily for at least three days and with at least one of the following: transitional rash, generalised lymphadenopathy, hepato- or splenomegaly or serositis.
Oligoarthritis	27–60% of children with JIA. One to four joints are affected within six months of onset. The most commonly affected joint is the knee, followed by the ankle. ANA antibodies are identified in most patients and uveitis in approx. 20% of children.
Polyarthritis (RF positive)	2–7% of children with JIA. Five or more joints are affected within six months of onset, usually symmetric, small joints of the hands and feet, and with a positive RF test result. Large joints, like the knee, ankle, hip and shoulder, may also be inflamed at the beginning of the disease (approx. one third of patients) but alongside the inflammation of small joints. In approx. one third of patients, rheumatoid nodules are present. In this subtype, erosions are most frequent, seen in almost all children within the first five years of the disease.
Polyarthritis (RF negative)	11–28% of children with JIA. Five or more joints, both small and large, can be affected within six months of onset, with two negative RF test results at least three months apart within six months of disease onset.
Psoriatic arthritis	2–11% of children with JIA. Arthritis and psoriasis, or arthritis and two or more of the following features are present: dactylitis, nail pitting, oil drop sign or onycholysis, or psoriasis in a first-degree relative. In the first stage of the disease, synovitis usually occurs in the knee, ankle, and metatarsophalangeal joints. Initially, only few joints are affected (oligoarthritis) and later, more joints may be involved (asymmetric polyarthritis). There are very characteristic changes of the hand and foot joints (as in adults with PsA).
Enthesitis-related arthritis (ERA)	5–10% of children with JIA. Arthritis and enthesitis, or arthritis or enthesitis with two or more of the following features: the presence or a history of SIJ tenderness or IBP; a positive HLA-B27 antigen; male over six years of age at onset; acute anterior uveitis or a family history of ankylosing spondylitis, ERA, sacroiliitis with IBD, reactive spondyloarthritis, or acute anterior uveitis in a first degree relative. Mostly affects boys. The most typical sign is enthesitis. Often, there are also traits of oligo- or polyarthritis, including the hip and other lower limb joints. The disease may have a mild course, affecting ≤4 joints, but in 30–40%, progression of the disease to sacroiliitis and spondylitis occurs.
Undifferentiated	Around 11–21% of children with JIA that does not fit the criteria of any of the other categories.

ANA – antinuclear antibodies; **ERA** – enthesitis-related arthritis; **HLA** – human leukocyte antigen; **IBD** – inflammatory bowel disease; **IBP** – inflammatory back pain; **PsA** – psoriatic arthritis; **RF** – rheumatoid factor; **SIJ** – sacroiliac joint.

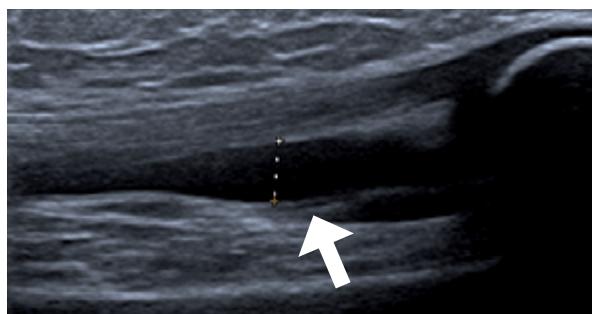


Fig. 1. Effusion in a knee joint in a 7-year-old girl, without synovial thickening (white arrow)

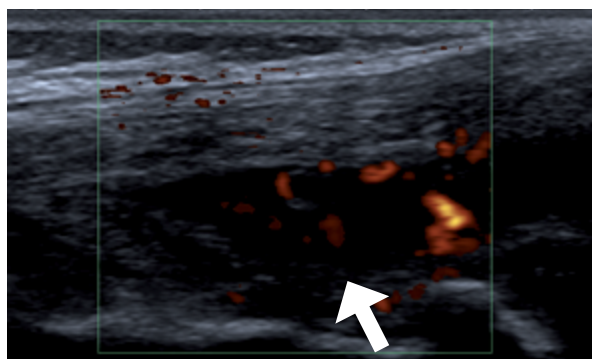


Fig. 2. Synovitis in a knee joint in a 10-year-old boy: thickened and highly vascularised synovium in power Doppler (white arrow)

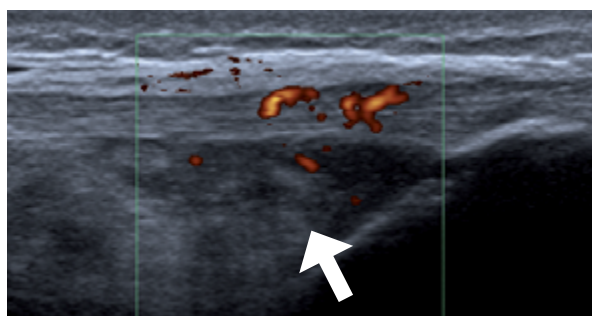


Fig. 3. Deep infrapatellar bursitis with moderate neovascularisation and secondary involvement of the patellar tendon (same patient as in Fig. 2; white arrow)

Such early findings can be diagnosed with ultrasound (US) or magnetic resonance imaging (MRI). The ability to precisely assess both the soft tissues and the bone, including bone marrow oedema, which may be an additional feature of early JIA, is an advantage of MRI over US and radiographs⁽⁹⁾. Malattia et al. compared MRI with other imaging techniques for the early identification of bone erosions in JIA. The study confirmed that MRI is superior; however, ultrasound is at least as good if not better than plain radiography at detecting cortical erosions in accessible regions⁽¹⁰⁾. Ultrasound examination has recently become widely popular and is currently the method of choice in the majority of cases when diagnostic imaging is necessary, including

the musculoskeletal (MSK) system. In patients with JIA, MSK ultrasound (MSUS) provides relevant information in the early stages of JIA, showing synovial and tenosynovial thickening, enhanced blood flow due to synovial or tenosynovial hypervascularity, as well as effusion in the joint cavity, tendon sheath and bursa (Fig. 1). This range of findings, which precede severe joint destruction, cannot be provided by classical plain radiography. These are classical findings in the early stage of JIA^(8,9).

Definitions of the most common pathological, inflammatory MSUS lesions seen in rheumatoid diseases were established by the European Society of Musculoskeletal Radiology (ESSR) and by the Outcome Measures in the Rheumatology (OMERACT) special ultrasound work group. The definitions include following lesions: synovitis, tenosynovitis and bone erosions^(11,12).

According to ESSR, active synovitis is characterised by neoangiogenesis developing in thickened synovium, often accompanied by effusions, which can be detected with power or colour Doppler (Figs. 2, 3). A four-grade semi-quantitative scoring system is recommended by ESSR to assess the severity of synovitis. It combines B-mode (grayscale) with colour/power Doppler⁽⁹⁾.

Bone erosions are seen as cortical bone defects and need to be visualised in two perpendicular planes. Erosions can involve vessels when active erosive disease is present (Fig. 4)⁽¹¹⁾. Tenosynovitis is defined as inflamed tendon sheath that is revealed as an effusion and tenosynovial thickening, with active neovascularisation (Fig. 5)⁽¹¹⁾.

OMERACT definitions published in 2005 were applied to adults, but were also used in children due to the lack of other relevant definitions. In 2019, the OMERACT ultrasound work group updated definitions of these elementary lesions, and distinguished paediatric synovitis, which is now defined as “the presence of hypoechoic synovial hypertrophy or the presence of synovial effusion”⁽¹²⁾. Distinction of paediatric synovitis was a response to the growing need for appropriate approach to JIA patients.

With respect to early diagnosis, ultrasound may also detect subclinical inflammation in JIA patients. In their study in eight adolescents with polyarticular or extended oligoarticular JIA, Favier et al.⁽¹³⁾ showed a 63% discrepancy between the documented rheumatologist's physical examination and an ultrasound exam. MSUS was more sensitive in detecting joint pathology when compared to physical examination. Ultimately, four patients (50%) had their therapy adjusted due to MSUS findings. Three out of four of them received biological treatment. Discrepancy between clinical and US examination was also found in a study by Hendry et al.⁽¹⁴⁾ among 30 children with JIA, where US often detected subclinical foot disease. Thus, sonographers should be aware that subclinical synovitis detected with MSUS is common in children with JIA⁽¹⁵⁾. There has also been a great promise in predicting JIA exacerbations by detecting subclinical synovitis with MSUS. Unfortunately, the results of prospective studies in children with subclinical synovitis seem

contradictory. Some publications indicate that detecting sub-clinical synovitis has some predicative values for detecting exacerbation, while other point out that there is very little or no value. Authors stress that there is a need for future studies which would focus specifically on different types of JIA⁽¹⁶⁾.

In addition to early diagnosis, MSUS is important in monitoring the disease activity and response to the treatment used. It also helps determine remission status of JIA patients⁽¹⁷⁾. The management of JIA has indeed improved after the incorporation of MSUS, which provides diagnostic and prognostic information and assesses patients' responses to therapy, especially with regard to erosions, effusions, synovitis, and tenosynovitis. The modality not only provides a quicker and dynamic visualisation of anatomical structures, but also has fewer complications and contraindications than other imaging techniques. Such information about disease activity and damage could not be gained by physical examination or plain radiography. The possibility of real-time imaging of a pathology can be reassuring to both the clinician and the patient. It can also be helpful when discussing treatment options^(18,19). A similar conclusion was drawn by Favier et al.⁽¹³⁾. They noticed that MSUS is a useful tool for education of patients, which improves their adherence to treatment recommendations. MSUS may play a key role in patients with rheumatic disorders, where benefits from treatment are delayed in time.

TECHNICAL CONSIDERATIONS

MSUS is still a developing technique. Linear transducers with frequencies up to 32 MHz allow high resolution and detailed imaging. Sensitive colour and power Doppler modalities as well as sonoelastography add additional diagnostic values to the exam.

Sonoelastography allows evaluation of tissue stiffness and has high sensitivity and high specificity in diagnosing different musculoskeletal disorders, including inflamed muscles and skin in juvenile dermatomyositis or scleroderma in children⁽²⁰⁾. Harmonic imaging utilises the phenomenon of non-linear propagation of US waves through the body, leading to multiple primary echo frequency returning from reflective body interfaces (harmonics) around the primary transducer frequency. Clearer images can be achieved when using this function.

The angle of insonation affects the imaging of tendons and muscles. Compound imaging is used to reduce angle related artifacts, such as anisotropy, which occurs when the beam is not perpendicular to a muscle fibre or a tendon and results in reduced echogenicity⁽⁴⁾. This ultrasound option uses automatic beam steering of a transducer array to obtain an image which corresponds with a perfect angle of insonation.

Fusion techniques which combine images from two different imaging modalities are also very promising ways to establish new protocol standards and recent trends on introducing artificial intelligence algorithms in diagnostic

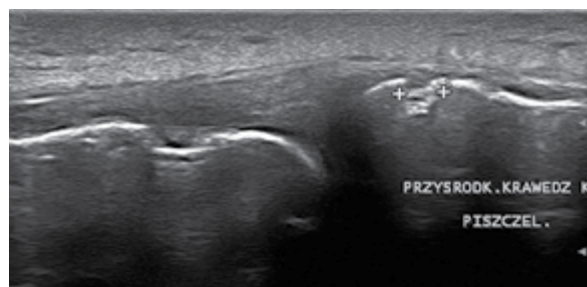


Fig. 4. Erosion of the medial margin of the tibia (crosses)

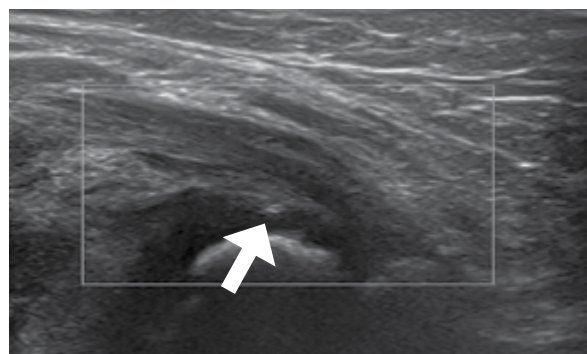


Fig. 5. Chronic tenosynovitis and tendinitis of the semimembranosus tendon in a 7-year-old boy (white arrow)

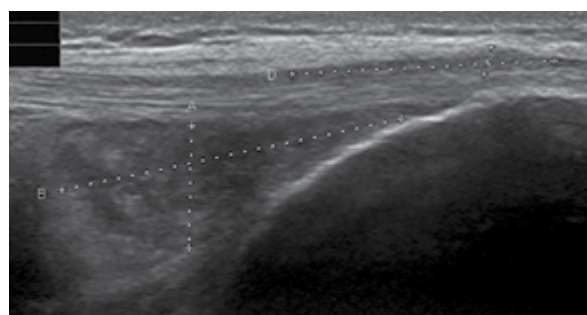


Fig. 6. Bursitis of the subcutaneous infrapatellar bursa (between crosses C and D) and the deep infrapatellar bursa (between crosses A and B) in a 17-year-old boy

imaging can facilitate the work with patients by shortening the time needed to make appropriate diagnosis.

Owing to the above achievements, ultrasound has a number of advantages in MSK imaging, including ease of use, good acceptance by the patients, wide availability, possibility of side-to-side comparison of symptomatic and asymptomatic side, low cost of the examination in comparison to other modalities such as MRI, and no necessity for contrast injections or sedation in children.

MSUS allows a real-time examination, multi-joint and dynamic study of structures, and can be performed at the bedside. For these reasons MSUS is widely used in JIA, where it can show soft tissues involvement and even, partially, bone abnormalities like cysts and erosions.

However, it must be noted that the examination of the entire joint space in ultrasound is not possible due to

acoustic shadowing from the overlying bone. Due to the limited ultrasound wave penetration, axial skeleton imaging is unfortunately compromised. In addition, US is an operator dependent imaging technique and significantly relies on the properties, quality and software of the machine used^(6,18).

The fact that this technique can ironically cause MSK symptoms among sonographers performing the aforementioned examinations is one of the most underestimated disadvantages of ultrasound. Sonographers very often perform US examinations in unnatural and forced positions. Long-term work can lead to functional overuse of the musculoskeletal system, resulting in joint pain, discomfort and even the need to take time off work in some cases. The pain in sonographers most often involves the spine, followed by shoulder and wrist⁽²¹⁾. High prevalence of MSK symptoms among sonographers forced scientists to begin research to mitigate and avoid these ailments by developing the so-called probe stabiliser, which enables fixation of an ultrasound probe to the body, thus helping to reduce MSK overload in ultrasound operators. Therefore, it is a promising tool in reducing work-related injuries in sonographers⁽²²⁾.

JIA MIMICKERS AND OTHER POSSIBLE FINDINGS IN MSUS

From the diagnostic point of view, the long list of mimickers, which need to be considered when performing US, also in children with JIA, is also important. None of the imaging features of JIA, including effusions, synovial thickening, bursitis, tenosynovitis, etc., is specific. For example, simple bursitis, which may be found in all age groups, is characterised by synovial thickening, increased amount of fluid within the bursa, localised pain near the inflamed area, and swelling of adjacent soft tissue. It may be caused by joint inflammation, but it also might result from a conflict between neighbouring MSK structures (Fig. 6)⁽²³⁾.

Other conditions which can mimic JIA synovitis include benign tumours, such as synovial osteochondromatosis, pigmented villonodular synovitis, synovial haemangioma, lipoma arborescens as well as malignant bone tumours in the initial stage. It is important that clinicians and radiologists are aware of the range of articular abnormalities that can masquerade as arthritis. This is particularly important when faced with a patient presenting with a monoarticular disease^(24,25).

There is also a large group of traumatic lesions, presenting with the same features as JIA like pain, swelling, limited movement. These symptoms should be particularly considered in children as the knee joint is the most frequent site of JIA and trauma. MSUS is used for the differential diagnosis of these symptoms in paediatric populations and allows to diagnose more pathologies as compared with clinical examination^(26,27). It is an ideal method to follow up muscle injury, monitor healing process as well as

identify complications, especially when using options such as colour/power Doppler and sonoelastography⁽²⁸⁾. Due to dynamic, real-time properties of the MSUS, it is the only diagnostic imaging technique that can identify muscle fasciculations, which are present in various rare conditions other than JIA, including neurological and musculoskeletal diseases, e.g. muscular dystrophy, neuralgic amyotrophy, as well as peripheral neuropathy⁽²⁹⁾.

In severe cases of JIA, cartilage destruction may be seen on MSUS. However, it must be noted that this finding is not specific for advanced JIA and may indicate a wide range of pathologies. The differential diagnosis should not only include pathological lesions or diseases, such as osteochondral lesions, or haemophilia, but also abnormalities altering biomechanical properties, which may generate cartilage damage. In the case of the knee joint, the Q-angle is defined as the direction of the force produced by the quadriceps muscle in the knee⁽³⁰⁾. Abnormal Q-angle value may result in force imbalance in the joint, leading to cartilage damage. These findings can deceptively imitate arthritis, especially when diagnosed at early stages⁽³⁰⁾.

Last but not least, young patients with more than one rheumatoid disease, i.e. the so-called overlapping syndrome, with similar/identical imaging findings on MSUS, may be encountered. Laboratory and serological tests and radiographs and/or MRI are needed for a diagnosis.

Therefore, precise diagnosis of rheumatic diseases in children often poses a significant challenge, and requires close collaboration between radiologists and clinicians. Also, further diagnostic imaging studies and laboratory tests are often necessary to confirm a particular clinical entity⁽³¹⁾.

CONCLUSIONS

MSUS is an easily accessible and non-invasive imaging modality which plays an important role in the diagnosis and follow-up of patients with JIA. Despite many advantages, ultrasonography has some limitations resulting from technical aspects and operator's subjectivity. Children and adolescents are not small adults; on the contrary, even in the MSK system there are developmental issues which need to be considered when making the diagnosis. Finally, there is a long list of differentials which ought to be considered, from benign (e.g. overload problems) to those most alarming (such as malignancies), often presenting with the same clinical picture in children.

Conflict of interest

The authors whose names are listed above certify that they have no affiliations with or involvement in any organisation or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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