Original paper

The primary role of radiological imaging in the diagnosis of rare musculoskeletal diseases. Emphasis on ultrasound

Federica Rossi[1], Carlo Martinoli[1,2], Giovanni Murialdo[3], Angelo Schenone[4], Marina Grandis[4], Diego Ferone[5], Alberto Stefano Tagliafico[1,2]

[1] Department of Health Sciences (DISSAL), University of Genova, Genoa, Italy
[2] Department of Radiology, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[3] Department of Internal Medicine, Policlinico San Martino University Hospital, University of Genoa, Genoa, Italy
[4] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, and Maternal and Child Health, University of Genova, Genoa, Italy
[5] Endocrinology, Department of Internal Medicine and Medical Specialties (DIMI), University of Genoa, Genua, Włochy

Correspondence: Alberto Tagliafico, MD, Department of Health Sciences, DISSAL, University of Genova, Via Pastore, 1, 16138 Genoa, Italy; tel.: +390105555248, fax: +390105556620, e-mail: albertotagliafico@gmail.com

Abstract

Objective: In July 2017 a multidisciplinary clinical Center specialized in rare diseases was activated. A rare disease can involve the musculoskeletal system. A multimodality musculoskeletal imaging approach allows for a rapid diagnosis. The purpose of this study was to assess when musculoskeletal radiology, ultrasound in particular, plays a primary role in the diagnostic path of a rare disease. **Methods and materials:** The Center included a list of 621 main rare diseases. Pathologies in which radiology has a primary diagnostic role were extracted from the list. From September 2017 to January 2018 all conditions involving the musculoskeletal system, including the peripheral nervous system, were systematically evaluated by one radiologist. The second radiologist, an official consultant of the Center, verified the list for consistency. Descriptive analysis was performed. **Results:** A total of 101/621 (16%) rare diseases can be diagnosed for the first time in the diagnostic path of the patient with medical imaging. A total of 36/101 (36%) rare diseases involve the musculoskeletal system. A total of 14/36 (39%) are pediatric diseases, 10/36 (28%) are adult age diseases, while 12/36 (33%) diseases affect all ages. A total of 23/36 (64%) of the selected rare diseases could be diagnosed with MRI, 19/36 (53%) with CT, 23/36 (64%) with X-ray, 9/36 (25%) with an US, and 1/36 (3%) with PET. **Conclusions:** Musculoskeletal imaging could be important for a non-invasive diagnosis in up to 36/101 (36%) rare diseases, as well as for outcome prediction, especially in pediatrics. Musculoskeletal imaging plays a crucial role in the diagnosis of rare diseases and could strongly influence the clinical pathway. Ultrasound is crucial in up to 25% of patients with rare diseases affecting the musculoskeletal system.

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Introduction

In July 2017, a clinical Center specialized in rare diseases was funded in our major University Hospital [1]. As defined by the European Union Regulation on Orphan Medicinal Products (1999), in European countries a disease is defined as rare when it affects fewer than 2000 people[2]. Even if a small number of people are affected by a single rare condition, rare diseases are not rare, at least in aggregate: there are between 5,000 and 8,000 rare diseases[3]. These pathologies are often serious, chronic, with a progressive and worsening course, and may be life-threatening. Rare diseases are also known as "orphan" diseases because the diagnosis is often very difficult or misinterpreted[4]. Indeed, the presenting signs and symptoms of rare diseases could be very different for individual patients and often mimic other pathologies. The diagnosis is often missed or frustratingly slow, thereby worsening the patients' physical and social status.

Indeed, it is well known that an early diagnosis of a disease may improve the prognosis and overall quality of life due to timely and appropriate therapies. Diagnostic imaging is usually performed and could be the most important diagnostic tool for several rare diseases. Medical imaging is crucial not only for the diagnosis, but also for therapy monitoring and even outcome prediction. Recent advances in several medical imaging techniques, such as magnetic resonance imaging (MRI), computed tomography (CT) and ultrasound (US), guarantee significant improvement in diagnosis due to improved sensitivity and tissue characterization. Most data provided by diagnostic imaging can also be immediately shared and transmitted by the radiologist to the referring physicians[5].

Rare diseases can involve all systems and organs, including the musculoskeletal system. Unfortunately, even in highly specialized environments with cutting edge resources such as genetics, many patients remain undiagnosed despite extensive medical evaluation. According to a recent study reported in the New England Journal of Medicine, the Undiagnosed Diseases Network yielded a rate of diagnosis of 35%[6]. Therefore, the purpose of the present study was to assess when medical imaging plays the primary role in the diagnosis of rare musculoskeletal diseases with an emphasis on ultrasound.

Materials and methods

The Center included an alphabetical database of 621 main rare diseases (with the main name as well as alternative names), based on the available data in the medical literature, to help patients with orphan diseases find detailed information about their conditions[1].

From September 2017 to January 2018 one junior radiologist under senior supervision (F.R. and A.T.) evaluated one by one all the 621 pathologies from the list to assess when radiology had a primary role in the diagnostic pathway. PubMed, Cochrane library, Medline (Ovid) and Orphanet databases were searched using appropriate keywords and following a strict scientific method. Different sources of information were compared. Rare diseases involving the musculoskeletal system were selected and classified based on age groups (adults, children, both adults and children) and etiologic sub-types. Further subdivision was made according to imaging modalities: magnetic resonance imaging (MRI), computerized tomography (CT), ultrasound (US), positron emission tomography (PET) and X-ray. The analysis was repeated twice to increase accuracy. A second senior radiologist (A.T.), official consultant of the Center, independently checked the list for consistency. Any discrepancies were resolved through discussion, until consensus was reached. To summarize the basic features of the obtained data, descriptive analysis was performed. Relevant US findings helpful for clinicians are systematically reported.

Results

The first part of the research involved a selection of rare diseases that could be diagnosed with an imaging approach. Musculoskeletal pathologies were selected and a subdivision into categories was performed for each abnormality (Tab. 1).

The role of medical imaging in the diagnosis of rare musculoskeletal diseases

A total of 101/621 (16%) rare diseases can be diagnosed for the first time with medical imaging.

A total of 36/101 (36%) rare diseases involve the musculoskeletal system, including the peripheral nervous system ($n = 8/36$, 22%).

Rare musculoskeletal conditions according to patients' age and etiopathology

Rare musculoskeletal diseases were subdivided according to the age of the affected population: 14/36 (39%) pediatric diseases, 10/36 (28%) adulthood diseases, 12/36 (33%) conditions affecting all ages. From the etiopathological point of view, the causes vary and are dominated by genetic ($n = 14/36$, 39%) and multifactorial ($n = 11/36$, 30.5%) factors. The exact cause of many rare diseases is still unknown ($n = 11/36$, 30.5%).

Rare musculoskeletal conditions according to the imaging technique

A total of 23/36 (64%) of the selected rare diseases could be diagnosed with MRI, 19/36 (53%) with CT, 23/36 (64%) with X-ray exams, 9/36 (25%) with an US scan, and 1/36 (3%) with PET.

Tab. 1. *Primary role of medical imaging in the diagnosis: list of selected rare diseases. Diagnostic modality (CT, US, MRI, PET, X-rays), patients' age, etiology of the rare diseases analyzed were considered. The names of rare conditions are indicated in the first column*

Disease name	Diagnostic Modality	Patients' age	Etiology
1.Achondroplasia	prenatal US, X-ray	Childhood	Genetic (autosomal dominant)[10]
2. Algodystrophy	X-rays, CT, MRI	All ages	Multifactorial
3. Buschke- Ollendorff syndrome	CT, X-ray	All ages	Genetic (autosomal dominant)
4. Claude Bernard Horner	CT, MRI	All ages	Multifactorial
5. CREST Syndrome	CT, X-ray	Adulthood	Multifactorial
6. Diffuse cutaneous systemic sclerosis	X-ray, CT	Adulthood	Multifactorial
7. Emery-Dreifuss muscular dystrophy	US, MRI	Childhood	Genetic (autosomal dominant or autosomal recessive or X-linked recessive)[11]
8. Ewing sarcoma	X-ray, CT, MRI	Childhood	Unknown
9. Fibrodysplasia ossificans progressiva	X-ray,CT	Childhood	Genetic (autosomal dominant)
10. Fibrous dysplasia	X-ray, CT	Childhood	Multifactorial
11. Focal myositis	MRI	Adulthood	Unknown
12. Gorham-Stout syndrome	CT, MRI, X-rays	All ages	Unknown
13. Inclusion body myositis	MRI	Adulthood	Unknown
14. Kienbok disease	X-ray, CT, MRI	All ages	Unknown
15. Klippel-Trenaunay-Weber syndrome	X-ray, CT, MRI	Childhood	Unknown
16. Larsen syndrome	X-ray	Childhood	Genetic (autosomal dominant)
17. Léri-Weill dyschondrosteosis	X-ray, CT	Childhood	Genetic (autosomal dominant)
18. Maffucci syndrome	X-ray, CT	Childhood	Unknown
19. McCune Albright syndrome	X-ray	Childhood	Genetic
20. Meralgia paresthetica	MRI, US	Adulthood	Multifactorial[12]
21. Multifocal motor neuropathy	MRI	Adulthood	Unknown
22. Multiple osteochondromas	X-ray, CT	Childhood	Genetic (autosomal dominant)
23. Nager syndrome	X-ray, prenatal US	Childhood	Genetic[13]
24. Nasu-Hakola disease	MRI, X-ray, CT	All ages	Genetic (autosomal recessive)
25. Neuralgic amyotrophy	MRI, US	Adulthood	Unknown[14,15]
26. Neurofibromatosis type 1	MRI	Childhood	Genetic (autosomal dominant)
27. Osteogenesis imperfecta	MRI, X-ray, CT	All ages	Genetic (autosomal dominant or recessive)
28. Osteopetrosis	MRI, X-ray, CT	All ages	Genetic (autosomal dominant or recessive or X-linked recessive)
29. Paget disease	MRI	Adulthood	Unknown
30. Peripheral neuropathy	MRI, US	All ages	Multifactorial[16]
31.Psuedoachondroplasia	X-ray	Childhood	Genetic (autosomal dominant)
32. Pudendal neuralgia	MRI, US	Adulthood	Multifactorial[17]
33. SAPHO syndrome	X-ray, CT, MRI	All ages	Multifactorial
34. Soft tissue tumor	PET, MRI, CT, US	All ages	Multifactorial[18]
35. Tarlov cysts	MRI, CT	Adulthood	Multifactorial
36. Tietze syndrome	X-ray, MRI, US	All ages	Unknown[19]
US – ultrasound, MRI – magnetic resonance imaging, CT – computed tomography, PET – positron emission tomography			

Tab. 2. *Main US findings and the role of US in the nine conditions where US may have an important contribution to diagnosis and even treatment*

Name of rare diseases according to orphanet database	Main US findings and US role	Genetic mutation
Achondroplasia and Nager syndorme	Early onset hydrocephalus, enlarged cerebellum and cisterna magna, and hydrancephaly on prenatal ultrasound	FGFR3 and SF3B4
Emery-Dreifuss	US identifies muscle fatty infiltration US assesses Achilles tendon	X (Xq28)
Muscular dystrophy and neuralgic amyotrophy	US identifies muscle fatty infiltration. Homogenously increased muscle echo intensity with attenuation of the US signal. Inflammatory myopathies can show homogenously increased echogenicity. Denervation can show „moth-eaten," atrophic muscles with fasciculation	Various
Meralgia paresthetica	Increased caliber of lateral femoral cutaneous nerve. Useful for infiltrative treatment	None, it is an entrapment syndrome
Peripheral neuropathy and pudendal neuralgia	Increased caliber of the nerve. Evaluation of the fascicular texture Evaluation of extraneural findings Guidance for infiltative procedures	NA
Soft Tissue Tumor	Lump detection Lump characterization US-guided biopsy Follow-up of superficial lesions	Depends on tumor sub-type
Tietze syndrome	Swelling of the costochondral joints and calcifications Corticosteroids injection	Unknown

Rare musculoskeletal conditions relevant to ultrasound

Table 2 presents the main US findings and the role of US in nine rare conditions where ultrasonography may have an important contribution to diagnosis and even treatment. These nine conditions are: achondroplasia, Emery-Dreifuss muscular dystrophy, meralgia paresthetica (Fig. 1 A, B), Nager syndrome, neuralgic amyotrophy, peripheral neuropathy (Fig. 2), pudendal neuralgia (Fig. 3), soft tissue tumor (Fig. 4), and Tietze syndrome.

Discussion

A wide range of rare conditions involve the musculoskeletal system. Rare musculoskeletal diseases can arise from genetic problems in the muscles themselves, like Duchenne muscular dystrophy, while other involve the nerves (e.g. Charcot-Marie-Tooth disease) or the bones (e.g. osteogenesis imperfecta). The absence of diagnosis represents an unmet medical need. Despite innovations in the clinical management of more common diseases, up to a quarter of patients diagnosed with a rare disease can have a diagnostic delay of between 5–30 years and 95 % of rare diseases are still without specific treatments[5]. The diagnosis of a rare musculoskeletal disease can be relatively rapid or slow. Some types manifest early in life with obvious and severe symptoms, while other emerge later. Patients with mild diseases might not notice any symptoms until later childhood or adulthood, delaying the diagnosis. Even if most rare conditions have congenital causes,

medical imaging plays an important and primary role in the diagnostic pathway. Indeed, although the progress of molecular genetics has improved, the selection of patients to undergo expensive genetic tests is often based on clinical imaging data. To the best of our knowledge, an evaluation of the role of radiology in the diagnosis of rare musculoskeletal diseases is missing in the literature. Groft underlined the growing interest in rare diseases with the expanding role and outreach activities of patient advocacy groups that have increased public awareness and legislative interest in rare diseases[10].

In the present paper, we identified several conditions where medical imaging generally plays a crucial role in the diagnosis. In particular, we identified nine conditions where US is crucial. Prenatal ultrasound is crucial to suspect the diagnosis before birth in acondorplasia and its variants, early onset hydrocephalus, enlarged cerebellum and cisterna magna, and hydrancephaly[11]. Nager syndrome, acrofacial dysostosis and temporomandibular joint disorders could be assessed with US as complementary tests[3]. In the case of Emery-Drayfus sindrome, which is present in the Orphanet database, US could be used to assess skeletal muscle and soft-tissue disorders, especially at the level of the Achilles tendons[12]. US is also helpful in muscular dystrophyes; indeed it is the only technique able to show fasciulations. In addition, ultrasound can identify abnormal echo intensity and size. US can be used to evaluate multiple muscles to guide not only the electrodiagnostic examination but also muscle biopsy if needed. Most muscular dystrophies show increased muscle echo intensity due to increased intramuscular fat and fibrosis[13]. Homogenously increased echogenicity is
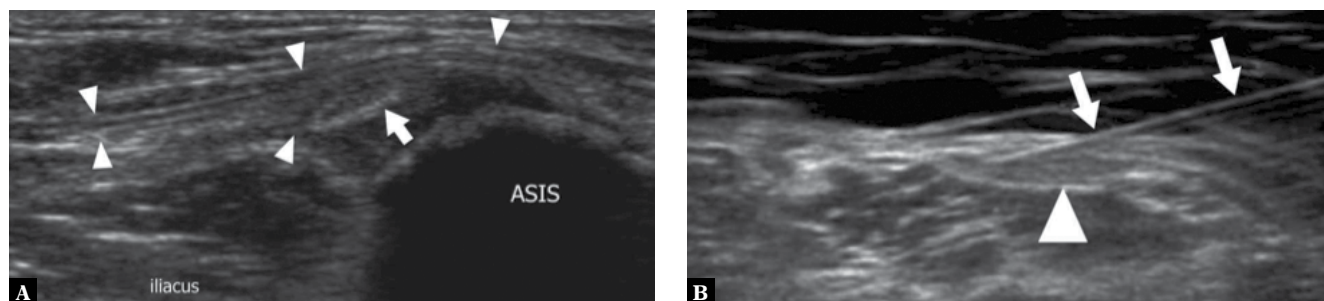
Fig. 1. **A.** *Short-axis sonogram over the anterior superior iliac spine (ASIS) showing the inguinal ligament (arrowheads) and the normal lateral femoral cutaneous nerve (arrow).* **B.** *Ultrasound-guided injection around the lateral femoral cutaneous nerve. Arrow: lateral femoral cutaneous nerve, arrowheads: needle. With permission from Tagliafico et al.*[7]
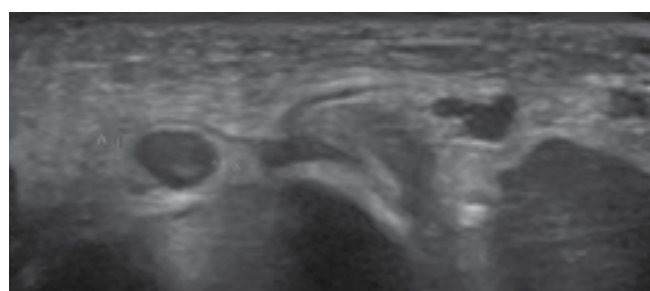
Fig. 2. *High-resolution US shows enlargement of an hypoechoic ulnar nerve (between calipers) in a post-traumatic mononeuropathy at the level of the medial epicondyle*
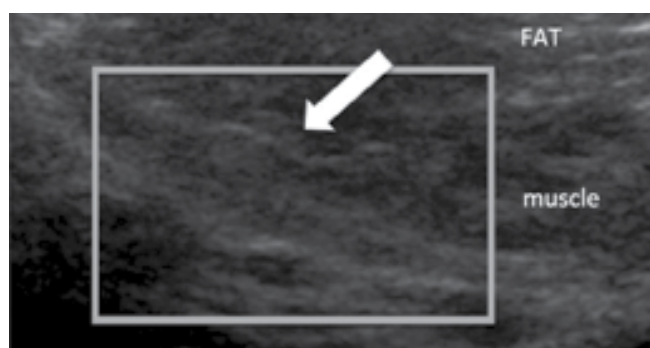
Fig. 3. *US images of a 35 year-old woman where oblique high-resolution US shows a focal area of enlargement and a hypoechoic area along the course of the pudendal nerve (white arrow) at the level of the distal Alcock canal. With permission from Tagliafico et al.*[8]
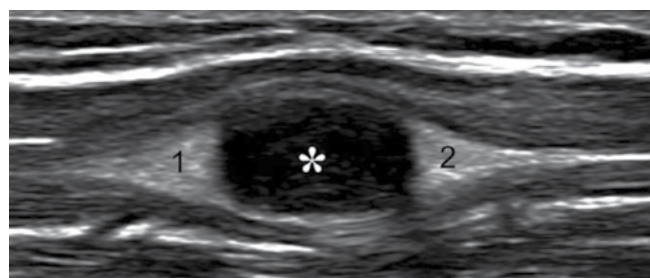
Fig. 4. *US images of the typical fat-split sign obtained with 22–2 MHz ultrasound on a soft-tissues tumor called small intramuscular schwannoma (asterisk) revealing a tapered cap of hyperechoic fat adjacent to the proximal (1) and distal (2) ends of the tumor. With permission from Tagliafico et al.*[9]

typical of inflammatory myopathies, but there is lack of signal attenuation in the first phases of muscular dystrophies. In denervation, typical "moth-eaten," atrophic muscles with fasciculations are seen[13]. The use of US to assess muscles in older and obese patients is limited. In general, muscle US yields sensitivities and specificities of 67% to 100% for detecting neuromuscular disorders in children[13].

Meralgia paresthetica is the entrapment of the lateral femoral cutaneous nerve at the inguinal ligament. At US, the nerve appears hypoechoic and swollen at the inguinal ligament[14]. US is helpful not only to confirm the entrapment, but is able to identify the underlying cause and guides interventional therapeutic procedure[14–16]. Medical literature is full of papers dealing with peripheral nerve ultrasound for both diagnosis and treatment[8,17–20]. We briefly underline that peripheral nerve US is an increasingly popular topic, with potential to detect abnormalities of the peripheral nerves even with quantitative measurements describing the internal fascicular echotexture. US can be also used to introduce the use of US as a possible quantitative imaging biomarker[19] by calculating quantitative parameters such as fascicular ratio or nerve density[19–21]. The role of US in patients with a soft-tissue mass is related to lump detection, characterization, follow-up and biopsy when necessary[22]. In the Tietze syndrome, an uncommon disease of unknown etiology that manifests with pain and tenderness of the parasternal joints, US can detect swelling of the costochondral joints, calcifications and guide corticosteroid injection[23].

Conclusions

In conclusion, medical imaging plays a primary role in the diagnosis of musculoskeletal rare diseases and should be considered as an important step in the diagnostic pathway. The presented data shows that musculoskeletal imaging could help diagnose specific rare musculoskeletal diseases, including peripheral neuropathies. Incentives for the development of preventive and validated diagnostic techniques are necessary and strongly recommended.

Conflict of interest

None of the authors have any financial disclosure or conflict of interest to declare.

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