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41-Year Systematic Literature Review of Early Infancy Osteomyelitis: What Have We Learned with the Entry of MRI into Diagnostic Protocol?

Barbara Minkowitz[1*], **Emily Lillie**[1], **Elizabeth Baorto**[2], **Robyn Murphy**[1], **Jennifer R Ristic**[1] **and Zachary Cherna**[1]

[1]*Department of Orthopedics, Morristown Medical Center, 100 Madison Avenue, Morristown, New Jersey 07960, USA*

[2]*Staff Physician, Grand Rounds, California, USA*

[*]**Corresponding author:** Barbara Minkowitz, Department of Orthopedics, Morristown Medical Center, 100 Madison Avenue, Morristown, New Jersey 07960, USA, Tel: +19732061033; E-mail: bminkowitz@aol.com

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Abstract

Background: A 41-year systematic literature review of early infancy osteomyelitis was performed. Observations were made regarding variables related to the diagnosis and treatment of the disease. We asked: 1) since magnetic resonance imaging (MRI) technology was introduced into diagnostic protocol in 1998, has there been an improvement in diagnosis and outcomes? 2) What additional aspects of the disease and diagnostic protocol may be affecting outcomes?

Methods: We performed a literature search and divided 36 cases into 2 groups; 1) all young infancy osteomyelitis cases before first reported MRI usage in 1998, 2) all young infancy osteomyelitis cases after first reported MRI usage in 1998. 34 cases from the literature and 2 of our cases were reviewed.

Results: Analysis of key variables related to diagnosis and treatment did not indicate statistically significant differences between the 2 groups. The following symptoms were common among both groups: pseudoparalysis in 28 (77.8%) and swelling in 22 (61.1%) patients.

Conclusion: Despite the benefits of MRI there have been few outcome changes with respect to the diagnosis and treatment of early infancy osteomyelitis. Early diagnosis is crucial; therefore, appropriate modifications to current diagnostic protocol may be warranted. Improvement may be possible if clinicians adopt a high index of suspicion for osteomyelitis and a low threshold of obtaining MRI.

Keywords: Early infancy osteomyelitis; MRI; Diagnostic protocol

Introduction

Osteomyelitis can present unique diagnostic and management challenges in neonates and young infants. Neonates are defined as less than 28 days-of-life (DOL). Infants up to 2 months of age were included. We describe the use of magnetic resonance imaging (MRI) to aid in the timely diagnosis of two of our own patients. Labs and vitals for these cases are presented (Table 1).

We also review case reports published over the past 41 years (Figure 1) to observe trends in symptoms, diagnostic methods, etiologic pathogens, and radiography to identify osteomyelitis (Tables 2 and 3). We asked: 1) since magnetic resonance imaging (MRI) technology was introduced into diagnostic protocol in 1998, has there been an improvement in diagnosis and outcomes? 2) What additional aspects of the disease and diagnostic protocol may be affecting outcomes?

	Case 1	Case 2*
Laboratory Test Results		
C-reactive protein (CRP) (reference range, 0.0-9.0) (mg/L)	Not available	4.1
Erythrocyte sedimentation rate (ESR) (reference range, 0-20) (mm/hr)	Not available	Not available
White blood-cell count (WBC) (reference range, 4.50-11.00) ($x10^3$ per nL)	17.02	12.51
Vital Signs		
Blood pressure (mm Hg)	90/60	77/33
Heart rate (beats/min)	116	132-172

Respiratory rate (breaths/min)	26	48-62
Temperature (°C)	37 (rectal)	36.2-36.9 (axillary)
Oxygen saturation, on room air	98%	97-100%
*Case 2 was admitted since birth in NICU - labs and vitals above are from DOL 54 when lower extremity edema was first noted		

Table 1: Laboratory results for our young infancy osteomyelitis patients

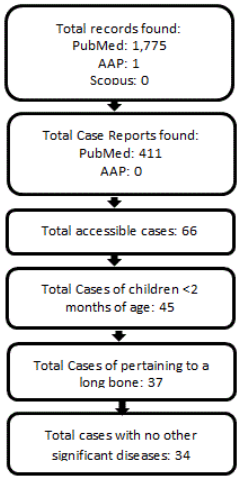

Figure 1: Flow chart of the research inclusion and exclusion method.

Materials and Methods

Literature search was performed using PubMed, AAP, and Scopus. Of the total records found, 1,775 were from PubMed, 1 from AAP, 0 from Scopus. Of the total case reports found 411 were from PubMed and 0 from AAP. 66 total cases were accessible. 45 of these cases included children <2 months of age. Of the 45 cases, 37 pertained to a long bone. 34 of these cases contained no other significant disease (Figure 1). In the end, 34 cases from the literature and our two cases were reviewed. These cases were divided into two groups; 1) all young infancy osteomyelitis cases before first reported MRI usage in 1998 (Table 2).

2) All young infancy osteomyelitis cases after first reported MRI usage in 1998 (Table 3). Groups consisted of 15 and 21 patients, respectively.

Case	Admittance age/Gender	Days symptomatic before admission	Pseudoparalysis/ limited mobility	Swelling	Radiographic Findings	Antibiotic treatment start time	Initial diagnosis	Final diagnosis	Sequelae
Henderson, et al. (Case 1) [1]	31 d/M	14 days	Left knee	Left knee	Left femur: lytic proximal femoral metaphysis and periosteal reaction distal left femur	Post-diagnosis of osteomyelitis	Suspected infection	Beta-hemolytic streptococcus Group B osteomyeltis	3 month follow-up, none reported
McCook, et al. (Case 1) [2]	28 d/F	2 days	Left arm	Left shoulder	N/A	Post-diagnosis of osteomyelitis	Osteomyelitis	Group B streptococcus osteomyelitis	6 week follow-up, none reported
McCook, et al. (Case 2) [2]	42 d/F	4 days	Right arm	Right shoulder	N/A	Pre-diagnosis of osteomyelitis	Suspected sepsis	Group B streptococcus osteomyelitis	3 month follow-up, none reported
McCook, et al. (Case 3) [2]	49 d/F	27 days	Left arm	Left shoulder	N/A	Post-diagnosis of osteomyelitis	Suspected infection	Group B hemolytic streptococcus osteomyelitis	Not reported
Svirsky-Fein, et al. (Case 1) [3]	19 d/M	Already in NICU	Right arm	Right shoulder, later bilateral knees	Right shoulder: lateral dislocation with lytic lesions of the proximal	Pre-diagnosis of osteomyelitis	Sepsis	Candida tropicalis osteomyelitis	1 month follow-up, none reported

					humeral metaphysis				
Svirsky-Fein, et al. (Case 2) [3]	14 d/M	Already in NICU	None	Right knee	Bilateral shoulder: left-widening of shoulder, lateral dislocation and lysis of humeral head also with lysis of right humeral head. Right knee: rarefaction at joint and metaphysis	Post-diagnosis of osteomyelitis	Sepsis	Candida tropicalis osteomyelitis	5 month follow-up, none reported
Broughton, et al. (Case 1) [4]	6 d/F	6 days	Right leg	Right knee	Right femur: lytic lesion distal metaphysis and demineralization adjacent epiphysis	Pre-diagnosis of osteomyelitis	Suspected infection	Type III Group B streptococcus osteomyelitis	17 months of age follow-up, none reported
Broughton, et al. (Case 2) [4]	10 d/M	8 days	Right arm and left leg	None	Left femur: metaphyseal lytic defects proximal femur with laterally displaced femoral head. Right shoulder: proximal humerus and left clavicle lytic lesions	Post-diagnosis of osteomyelitis	Suspected infection	Group B streptococcus osteomyelitis	9 month follow-up, none reported
Broughton, et al. (Case 3) [4]	28 d/F	14 days	Bilateral arms	None	Bilateral shoulders: lytic defects proximal humeral metaphyses crossing into the epiphysis	Pre-diagnosis of osteomyelitis	Suspected infection	Osteomyelitis, suspected Type III Group B streptococcus.	Not reported
Isaacs, et al. (Case 1) [5]	10 d/M	Unknown	Left arm	Developed in left shoulder, right foot, left groin, and left thigh	Left shoulder: lytic lesion humeral metaphysis, later showed chronic osteomyelitis left humeral metaphysis and periosteal reaction left femur	Pre-diagnosis of osteomyelitis	Erb's palsy	Staphlococcus aureus and coliforms osteomyelitis	Follow-up, none reported
Isaacs, et al. (Case 2) [5]	14 d/F	Unknown	Left arm	Developed in left arm	Left humerus: lytic lesion humerus with periosteal reaction	Post-diagnosis of osteomyelitis	Erb's palsy	Group B streptococcus osteomyelitis	2 month follow-up, none reported
Isaacs, et al. (Case 3) [5]	17 d/M	Already in NICU	None	Left thigh, right shoulder and wrist, and left middle finger	N/A	Time N/A	Suspected infection	Staphlococcus aureus osteomyelitis	9 month follow-up, head and neck of left femur were totally destroyed, left thigh was shorted by 1 cm, and limited dorsiflexion of

									right wrist and flexion contracture of left proximal interphalangeal joint
Orebaugh, et al. (Case 1) [6]	28 d/M	14 days	bilateral legs	None	Lower extremities: bilateral distal femoral periosteal reaction and osteolysis.	Post-diagnosis of osteomyelitis	Osteomyelitis and secondary pyarthrosis	Staphylococcus aureus osteomyelitis	2 week follow-up, none reported
Obando, et al. (Case 1) [7]	3 d/F	Already in NICU	Left leg and ankle	None	N/A	Pre-diagnosis of osteomyelitis	Acute neuropathy	Group B streptococcus osteomyelitis	5 month follow-up, none reported
Oleinik, et al. (Case 1) [8]	20 d/M	Already in NICU	None	Left elbow	Left humerus: lucency distal humerus, erosion of olceranon, periosteal reaction	Pre-diagnosis of osteomyelitis	Suspected infection	Candida lusitaniae and amphotericin ostoemyelitis	6 month follow-up, none reported

Table 2: All young infancy osteomyelitis cases before first reported MRI usage in 1998.

Case	Admittance age/ Gender	Days symptomatic before admission	Pseudoparalysis/ limited mobility	Swelling	Radiographic or MRI Findings	Antibiotic treatment start time	Initial diagnosis	Final diagnosis	Sequelae
Sadlier and Connolly (Case 1) [9]	3 d/M	Already in NICU	Left arm	Later in left shoulder	Left humerus xray: lytic lesion humerus	Post-diagnosis of osteomyelitis	Traumatic brachial-plexus injury	Group B streptococcus osteomyelitis	3 month follow-up, none reported
Sadlier and Connolly (Case 2) [9]	15 d/M	2 days	Left arm	None	MRI normal	Post-diagnosis of osteomyelitis	Traumatic brachial-plexus injury	Group B streptococcus osteomyelitis	Follow-up, neurologically normal
Sadlier and Connolly (Case 3) [9]	21 d/F	18 days	Left arm	Later in left shoulder	Left shoulder xray: demineralization humeral head	Post-diagnosis of osteomyelitis	Traumatic brachial-plexus injury	Group B streptococcus osteomyelitis	5 month follow-up, none reported
Wathne, et al. (Case 1) [10]	5 d/M	Unknown	None	Left toe, left ankle, and chin	MRI normal	Pre-diagnosis of osteomyelitis	Sepsis	Beta-hemolytic streptococcus group A osteomyelitis	4 month follow-up, none reported
Wathne, et al. (Case 2) [10]	12 d/M	Unknown	Right leg	None	Right leg MRI: marrow edema distal femur	Post-diagnosis of osteomyelitis	Suspected infection	Osteomyelitis, culture negative	1 month follow-up, none reported
Wathne, et al. (Case 3) [10]	21 d/F	Unknown	Right leg	None	Right hip MRI: effusion hip with some light signal changes in caput femoris	Post-diagnosis of osteomyelitis	Arthritis/ osteomyelitis	Osteomyelitis, culture negative	1 month follow-up, none reported

Solebo, et al. (Case 1) [11]	14 d/M	7 days	Right arm	None	Right shoulder xray: lytic area humeral head and radioisotope 'hot spot'	Post-diagnosis of osteomyelitis	Erb's palsy	Osteomyelitis, causitive pathogen not reported	4 month follow-up, none reported
Estienne, et al. (Case 1) [12]	13 d/M	8 days	Right and eventually left arm	None	Right shoulder xray: edema humeral head	Post-diagnosis of osteomyelitis	Suspected infection	Osteomyelitis, culture negative	6 month follow-up, X-rays revealed mild avascular necrosis
Liao, et al. (Case 1) [13]	31 d/F	24 days	Right shoulder and arm	Right shoulder	Right humerus xray: large osteolytic lesion proximal humeral metaphysis, MRI consistant	Post-diagnosis of osteomyelitis	Erb's palsy	Klebsiella pneumoniae osteomyelitis and septic synovitis	2 month follow-up, almost full recovery
Korakaki, et al. (Case 1) [14]	15 d/F	Unknown	Left knee	Left leg	Left leg MRI: consistent with acute osteomyelitis left tibia septic arthritis knee joint	Pre-diagnosis of osteomyelitis	Suspected infection	MRSA osteomyelitis and septic arthritis	1 year follow-up, none reported
Korakaki, et al. (Case 2) [14]	28 d/M	5 days	None	Left lateral chest wall and left knee	Rib xray: lytic lesions 10th rib and distal metaphysis left femur with new bone formation. Ultrasound revealed edema of the soft tissue	Post-diagnosis of osteomyelitis	Acute osteomyelitis and septit arthritis	MRSA osteomyelitis and septic arthritis	2 year follow-up, limp, 2 cm discrepancy left lower limb, flexion deformity of the left knee joint and ankylosis
Waseem, et al. (Case 1) [15]	21 d/F	Unknown	Right arm	None	Right shoulder MRI: shoulder joint effusion	Post-diagnosis of osteomyelitis	Erb's palsy	Osteomyelitis, culture negative	At follow-up, none reported
Qadir, et al. (Case 1) [16]	35 d/M	14 days	Right arm	Right shoulder joint	Right shoulder xray: periosteal reaction proximal humerus and irregularity proximal humeral metaphysis	Post-diagnosis of osteomyelitis	Suspected infection	Klebsiella pneumoniae osteomyelitis	7 month follow-up,clinically normal; right humeral head smaller than left
Winkler, et al. (Case 1) [17]	18 d/F	Unknown	Right arm	None	MRI: edema marrow clavicle with periosteal abscess and fluid extension into the sternoclavicular joint	Pre-diagnosis of osteomyelitis	Suspected infection	MSSA osteomyelitis	2 year follow-up, none reported
Allagui, et al. (Case 1) [18]	28 d/M	10 days	Left shoulder	Near clavicle	Left shoulder ultrasound: left supraclavicular collection corresponding to a subperiosteal abscess	Post-diagnosis of osteomyelitis	Suspected infection	Haemophilus influenzae osteomyelitis	None reported

Berkowitz, et al. (Case 1) [19]	28 d/F	7 days	Left leg	None	Left leg MRI: edema marrow distal tibial osteomyelitis and effusion ankle joint	Post-diagnosis of osteomyelitis	Suspected infection	Group B streptococcus osteomyelitis	Not reported
Dessie and Constantine (Case 1) [20]	28 d/F	1 day	None	Right thigh	Right leg MRI: 1-cm intraosseous fluid collection in the right distal femoral metaphysis, extending into epiphysis and knee joint	Post-diagnosis of osteomyelitis	Suspected infection	Group B streptococcus osteomyelitis	None reported at discharge
Ben-Meir, et al. (Case 1) [21]	35 d/F	7 days	Bilateral arms	None	MRI: extensive edema involving C5, adjacent intervertebral discs, epidural space from C6 to the clivus, paravertebral space at C1–C4, neck and pharyngeal soft tissue	Pre-diagnosis of osteomyelitis	Suspected infection	MSSA osteomyelitis	4 month follow-up, mild flattening of C5 vertebra with complete resolution of inflammation
Zhan, et al. (Case 1) [22]	28 d/M	Unknown	None	Right leg, worse over time	Right leg MRI: significant soft tissue edema and destruction of the right distal tibia and periosteal reaction of the right distal tibia and fibula	Pre-diagnosis of osteomyelitis	Suspected sepsis	Salmonella typhi osteomyelitis	3 month follow-up, none reported
Present (Case 1)	28 d/M	7 days	Left arm	None	Left arm MRI: fluid in elbow joint, edema of distal humerus, proximal radius, olecranon, lysis of the distal humerus	Pre-diagnosis of osteomyelitis	Arm sprain	MRSA osteomyelitis and septic elbow	3 year follow-up, elbow lacked 15 degree flexion and continued defect from initial lytic lesion of the humerus
Present (Case 2)	54 d/M	Already in NICU	None	Left leg	Left leg MRI: abscess of the left tibia and fibula, fluid crossing into the epiphysis	Pre-diagnosis of osteomyelitis	Osteomyelitis	Osteomyelitis, suspected Group B streptococcus	5 year follow-up, none reported

Table 3: All young infancy osteomyelitis cases after first reported MRI usage in 1998.

Case 1

4-week-old male with 5-day neonatal intensive care unit (NICU) stay for respiratory distress and polydactyly with supernumerary finger stub removal at birth presented with progressive upper extremity pseudoparalysis. After 7 symptomatic days, he was admitted to an outside hospital emergency department (ED). The x-ray and labs were normal, and he was sent home with an "arm sprain", despite pseudoparalysis.

After 11 symptomatic days, the elbow and arm became edematous and the infant became irritable. Radiographs repeated by the pediatrician showed bony destruction within the left distal humeral metaphysis demonstrating osteomyelitis. Initial vitals and labs are in Table 1.

MRI with gadolinium was consistent with septic elbow and osteomyelitis of the distal humerus, proximal radius, and olecranon. The patient was taken to the operating room (OR) where he underwent

elbow irrigation and debridement (I&D) with packing. The humeral supracondylar area contained yellow and lobulated pus.

He was treated with cefotaxime and vancomycin, postoperative vitals are shown in Table 1. I&D was repeated 3 days later with wound closure. Methicillin-resistant *Staphylococcus aureus* (MRSA) sensitive to clindamycin was identified. Blood cultures were negative. He was discharged on POD 4 and treated with 6-weeks intravenous clindamycin. At 3-year follow-up, the elbow lacked 15 degrees flexion. X-rays showed bone defect filling in.

Case 2

Male at 27 3/7 week twin gestation was admitted to the NICU for late-onset Group B streptococcus sepsis at DOL 17. He was treated with a 21-day course of ampicillin and intubated for poor oxygenation. Leg swelling was observed on DOL 54. Labs and vitals are presented (Table 1). Initial radiograph was normal. Follow-up radiograph on DOL 58 showed metaphyseal lucency with periosteal reaction suggestive of proximal tibial osteomyelitis. He was started on cefotaxime and vancomycin.

Orthopedic surgery was consulted. MRI demonstrated abscess of the tibia and fibula, fluid crossing into the epiphysis. An abscess containing clear fluid with fibrinous material was debrided around the proximal tibia and distal femur. Drill holes were made into the tibia epiphysis and metaphysis. OR cultures were negative. He was given a 6-week course of ampicillin for presumed Group B streptococcus and discharged on DOL 95. At 5-year follow-up, plain radiographs show the growth plate functioning with no central irregularity.

Results

Between the two groups, most common symptoms were pseudoparalysis, in 28 (77.8%), and swelling, in 22 (61.1%) patients. 14 (38.9%) patients experienced both symptoms; all experienced one. 11 (30.6%) were febrile. Patients were between 3 and 54 DOL (average 22 DOL).

In Group 1 (cases before first reported MRI usage in 1998; Table 2), 8 (53.3%) patients are male and 7 (46.7%) are female. In group 2 (cases after first reported MRI usage in 1998; Table 3), 12 (57.1%) patients are male, and 9 (42.9%) are female.

A comparison and analysis of key diagnostic variables between the 2 groups are presented (Table 4). The results indicated no statistical significance.

	Group 1 (All young infancy osteomyelitis cases before first reported MRI usage in 1998) (n=15)	**Group 2 (All young infancy osteomyelitis cases after first reported MRI usage in 1998) (n=21)**	**p-value**
Average time between initial symptoms and admission	11 days (8 patients)	9.2 days (12 patients)	0.6407 Mann Whitney
Required surgery	6 patients (40%)	10 patients (47.6 %)	0.741
Initially misdiagnosed	6 patients (40%)	9 patients (42.9%)	>0.999
Misdiagnosed with Erb's palsy or neuropathy	3 patients (20%)	3 patients (14.3%)	0.677
Began antibiotic treatment before diagnosis	7 patients (50%)	7 patients (33%)	0.499
Causative pathogen is streptococcus B	8 patients (53%)	5 patients (23.8%)	0.090
Causative pathogen is ***Staphylococcus aureus***	3 patients (20%)	5 patients (23.8%)	>0.999
Negative cultures	1 patient (6.7%)	5 patients (23.8%)	0.367
Reported sequelae	1 patient (6.7%)	4 patients (19%)	0.376
Average time from admission to correct diagnosis	Not available	10.3 days (10 patients)	

Table 4: Key diagnostic variables.

Discussion

We asked: 1) since magnetic resonance imaging (MRI) technology was introduced into diagnostic protocol in 1998, has there been an improvement in diagnosis and outcomes? 2) what additional aspects of the disease and diagnostic protocol may be affecting outcomes?

Over the past 41 years, despite the introduction of MRI into diagnostic protocol in 1998, diagnosis and treatment of early infancy osteomyelitis have not significantly changed. There is a low incidence of early-infancy osteomyelitis. Signs and symptoms are difficult to discern [23-25]. Prompt diagnosis and treatment are crucial [26-28].

Earlier diagnosis mitigates serious sequelae, such as cartilage destruction, bone and growth plate deformity, joint dislocation, limited joint motion, and neurologic abnormalities [29-31]. A flow chart (Figure 2) highlights common time points for diagnostic delay.

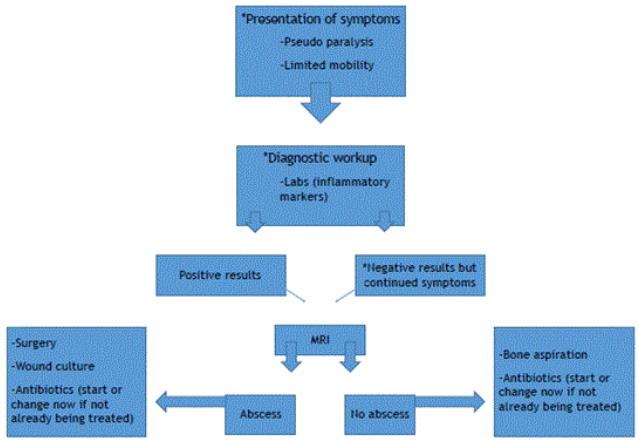

Figure 2: Diagnostic flow chart for early childhood osteomyelitis. Potential for diagnostic delay is indicated for the following time points: presentation of symptoms, diagnostic workup, and negative results.

Duration of symptoms before admission remains about the same, which may be unavoidable since parents are responsible for presenting during this subtle phase. Of the reported cases, patients were admitted after an average of 10 symptomatic days and diagnosed after 10 additional days (Tables 2 and 3). Fever occurs in one third or fewer cases [23,29]. Pseudoparalysis or extremity swelling are present in 60-95% of infections and should alert the clinician to possible osteoarticular infection [23-25]. Pseudoparalysis present at birth is indicative of a neurological problem or Erb's palsy; however, pseudoparalysis which develops after birth indicates infection. There was a decrease in patients misdiagnosed with neuropathy after the use of MRIs, although about the same number of patients was misdiagnosed in general.

Radiologic abnormalities may be absent, subtle, or only positive in chronic infections when lytic lesions, sequestrum, or involucrum are present [23]. MRI is useful in defining bone edema, soft tissue involvement, delineating bone and soft tissue abscesses, and showing co-existing joint pathology [32,33]. MRI is the most sensitive radiological investigation for diagnosing osteomyelitis and can detect osteomyelitis 1 to 3 days post-infection [24,32].

Radiographs cannot pick up signs of osteomyelitis until after 2 weeks when the infection is chronic [32,34,35]. To prevent delay, MRI should be ordered immediately once patients develop pseudoparalysis, regardless of "normal" radiographs. MRI should not delay diagnosis, but rather hasten it and improve certainty of the underlying disorder.

Neonates are often treated empirically with broad spectrum antibiotics. Ideally, pathogen identification should be sought to optimize treatment with antibiotics. Continued advancements in PCR-based testing will enable pathogen identification to occur with higher degrees of specificity, sensitivity, and rapidness [36]. More aggressive pathogen analysis and treatment is warranted and will be especially helpful for treating neonates.

Despite the evident value of using MRI technology, the natural history of early infancy osteomyelitis may be impossible to avoid. However, an in-depth understanding of the disease and common time points of diagnostic delay may give insight as to why outcomes are not improving as one might expect. Optimizing diagnostic protocol may be warranted if it will lead to clinicians lowering the threshold for attaining MRI and utilizing the technology earlier in their patient assessments. Emphasis on early diagnosis appears to be crucial for improving outcomes.

Statement of Informed Consent

Both patients' parents were informed that the case data would be submitted for publication, to which they agreed.

Disclosures

The authors have no disclosures or conflicts of interest.

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