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ORIGINAL ARTICLE

Can early MRI distinguish between *Kingella kingae* and Gram-positive cocci in osteoarticular infections in young children?

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Abstract
Background *K. kingae* is a common causative organism in acute osteoarticular infections (OAIs) in children under 4 years of age. Differentiation between *K. kingae* and Gram-positive cocci (GPC) is of great interest therapeutically.
Objective Our aim was to identify early distinguishing MRI features of OAIs.
Materials and methods Thirty-one children younger than 4 years of age with OAI underwent MRI at presentation. Of these, 21 were caused by *K. kingae* and ten by GPC. Bone and soft tissue reaction, epiphyseal cartilage involvement, bone and subperiosteal abscess formation were compared between the two groups. Interobserver agreement was measured.
Results Bone reaction was less frequent ($P = 0.0066$) and soft tissue reaction less severe ($P = 0.0087$) in the *K. kingae* group. Epiphysis cartilage abscesses were present only in the *K. kingae* group ($P = 0.0118$). No difference was found for bone abscess ($P = 0.1411$), subperiosteal abscess ($P = 1$) or joint effusion ($P = 0.4414$). Interobserver agreement was good for all criteria.
Conclusion MRI is useful in differentiating *K. kingae* from GPC in OAI. Cartilaginous involvement and modest soft tissue and bone reaction suggest *K. kingae*.

Keywords Paediatric osteoarticular infections · *Kingella kingae* · Gram-positive cocci · MRI

Introduction

Diagnosis of acute osteoarticular infection (OAI) in children remains a challenge. It requires high clinical alertness and cannot be ruled out in the absence of fever or by normal laboratory results [1]. Efficient treatment requires early diagnosis with identification of the causative organism [2–4], but this is only possible in 40–70% of paediatric OAIs [5–7] and even more difficult in children younger than 4 years [8] in developed countries. *Staphylococcus aureus* and *Streptococcus* species are reported to be the major pathogens of paediatric OAI [6, 9–12]. However, recently, a Gram-negative bacillus, *K. kingae*, has been reported as a frequent causative organism in children under 4 years of age [4, 13–16]. The infection usually generates only a mild inflammatory response unless accompanied by endocarditis [17]. The clinical and biological inflammatory responses to *K. kingae* infection are often mild to moderate, and affected children often have few signs and symptoms of OAI. *K. kingae* is difficult to isolate on solid media, and synovial aspirates and bone biopsies are culture-negative in a substantial proportion. A new real-time polymerase chain reaction (PCR) assay targeting a toxin (RTX) gene [5, 8, 15, 18] appears helpful to confirm clinically suspected *K. kingae* OAI.

It is widely accepted that early MRI is helpful in the management of acute OAI. It is reliable for assessing the

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viability and blood flow to the infected bone, for identifying bone and soft tissue abscesses needing surgical treatment, for detecting joint effusion or distention of the capsule and for directing biopsies. MRI is also useful in the diagnosis of arthritis and in distinguishing different types of arthritis [19–22].

Our study was designed to investigate possible MRI features specific for *K. kingae* OAI in young children, thereby helping to differentiate this infection from OAI caused by Gram-negative cocci (GNC). This would allow early and tailored management. The management of *K. kingae* OAI is less aggressive. Most of the time, there is no need for surgical lavage or debridement of the affected bone or joint, whereas it is always required for Gram-positive cocci (GPC), especially for *Streptococcus* or *Staphylococcus* species. *K. kingae* is highly susceptible to penicillin, ampicillin, second- and third-generation cephalosporins, macrolides, co-trimoxazole, ciprofloxacin, tetracycline, and chloramphenicol [23]. It has decreased susceptibility to oxacillin, and appears fully resistant to trimethoprim and to vancomycin [24–27]. Finally, the duration of intravenous treatment (approximately 48 h for *K. kingae*) and subsequent oral treatment differs.

Imaging criteria allowing differentiation between *K. kingae* and GPC in OAI may be useful for early diagnosis and optimisation of treatment, especially in cases where MRI is performed before bacteriological results become available.

Materials and methods

After approval by the institutional review board, one of the authors (D.C.) reviewed medical records of children younger than 4 years of age admitted to our tertiary care hospital from January 1999 to June 2010 with a final diagnosis of acute OAI, who had undergone MRI at presentation.

Criteria established by Morrey et al. [28, 29] were used to estimate the risk of having a bone or joint infection in suspected children. OAI was defined as bone (osteomyelitis) or joint (septic arthritis) infection or both (osteomyelitis with septic arthritis). Only children with a confirmed bacteriological diagnosis of *K. kingae* or GPC were included. Children with spinal OAI were not included.

Clinical and biological investigations

Blood, joint fluid or bone aspirate cultures were ordered for each patient and the media incubated for 10 days. To investigate *K. kingae* OAI, initial aliquots (100–200 µl) were stored at -80°C until processing for DNA extraction. A novel real-time PCR assay targeting the RTX toxin gene was used in this study (Roche Molecular Biochemicals, Mannheirm, Germany). The assay is designed to detect two gene targets from the *K. kingae* RTX toxin locus, namely genes *rtxA* and *rtxB*, and results are available after 72 h [8].

Imaging

MRI was performed within 48 h of admission at a mean interval of 3.5 days (SD, 5 days) from symptom onset. All examinations were performed before any other invasive procedure, such as joint fluid aspirate or bone biopsy.

MRI was performed under sedation or general anaesthesia in children 6 months to 6 years of age. In children younger than 3 months old, MRI was performed during sleep after feeding.

All MRI studies were performed with a 1.5-T Avanto scanner (Siemens Medical Solutions, Erlangen, Germany). A dedicated body coil was used for imaging of the pelvis or long appendicular bones and a dedicated knee coil for the knee. For other regions, flexible surface coils were used.

The MRI protocol included coronal T1-weighted turbo spin echo sequences (TR/TE, 500/12 ms), axial T2-weighted turbo spin echo (TR/TE, 6,420/99 ms), 3-D inversion recovery (inversion time = 160 ms) T2-weighted turbo spin-echo (SPACE; TR/TE, 2,000/201 ms; isotropic voxel dimensions, 1.3-1.5 mm), and coronal (TR/TE, 639/13 ms) and axial (TR/TE, 350/8.8 ms) fat-suppressed T1-weighted spin-echo after intravanous administration of gadoteric acid (Dotarem; Guerbet, Roissy CdG, France) at a dose of 0.1 mmol/kg body weight. Contrast-enhanced images were obtained immediately after contrast injection. Field of view, matrix and slice thickness depended on the size of the anatomical area of interest.

Image analysis

One author (D.C.) anonymised the MRI studies performed at the time of presentation, which were coded and transferred to a dedicate computer station and stored in random order. Two radiologists (A.K. and L.M.) retrospectively and independently reviewed all MRI investigations. One reader was an experienced paediatric radiologist; the other was a paediatric radiology fellow. The readers were blinded for all clinical and radiological data except patient age and clinical suspicion of OAI. Imaging evaluation criteria and score scale were established by one radiologist (D.T.) in consensus with the two readers, based on the literature [7]. MR images were analysed for joint effusion, soft tissue reaction/abscess, increased signal intensity of bone on water-sensitive sequences (bone reaction), bone abscess, subperiosteal abscess and cartilaginous involvement/abscess. A four-point scale (absent, slight, moderate, marked) was used to grade the presence of soft tissue and

bone reaction [7]. The amount of joint fluid was considered either normal or abnormal. Soft tissue reaction was defined as areas of increased soft tissue (subcutaneous fat or muscles) intensity on water-sensitive sequences and abnormal contrast-enhancement. Bone reaction was defined as areas of increased marrow intensity on water-sensitive sequences, and either increased or decreased marrow intensity on contrast-enhanced T1-weighted images. Intraosseous, subperiosteal and soft tissue abscesses were defined as well-circumscribed lesions of fluid intensity on water-sensitive sequences and low intensity on T1-weighted images, with peripheral contrast-enhancement. Cartilaginous (physis and epiphysis) involvement was characterised by increased signal intensity or widening of the growth plate on water-sensitive images and increased or decreased overall enhancement or rim enhancement.

Two separate patient groups were established on the basis of the bacteriological diagnosis, OAI due to *K. kingae* and OAI due to GPC. MRI findings were compared between the groups.

Statitical analysis

The agreement between the two readers was assessed by Cohen's kappa and the confidence intervals given. The value of kappa was interpreted on the Landis and Koch scale (0.0-0.2: slight agreement; 0.21-0.40: fair agreement; 0.41-0.60: moderate agreement; 0.61-0.80: substantial agreement; 0.81-1.00: almost perfect agreement).

For each reader, the variables were compared between groups by the Fisher exact test. The significance level was set at 0.05. The statistical analysis was performed with the free software R (Project for Statistical Computing) and with freely available tools at http://faculty.vassar.edu/lowry/kappa.html.

In the further statistical evaluation, when there was a difference between observers, the result of a reached consensus was used.

Sensitivity, specificity, positive predictive value and negative predictive value of MRI for the diagnosis of *K. kingae* OAI were also calculated.

Results

Clinical characteristics

Thirty-one children (14 females) were included in the study. All had clinical signs of non-spinal OAI, underwent MRI in the acute phase of symptoms and had a confirmed bacterial diagnosis of *K. kingae* or GPC. There were no children with methicillin-resistant *Staphylococcus aureus* infection. Mean age was 19.6 months (range, 1-48 months; SD, 14.8 months). Twenty-one were positive for *K. kingae* and ten for GPC.

The mean interval from symptom onset to MRI was 3.5 days (SD, 5 days).

The most frequently involved location was the shoulder (n = 7), followed by the hip (n = 6) and the foot (n = 5). Ankle, knee, wrist and elbow were equally affected (n = 3 for each). One child had clavicle involvement. Seventeen children had findings of osteomyelitis (11 in the *K. kingae* group and six in the GPC group), whereas 14 had findings of arthritis (ten in the *K. kingae* group and four in the GPC group)

MRI findings

Interobserver reliability was high in both patient groups for soft tissue involvement (κ = 0.7634, 95% CI = 0.5734-0.9534), joint effusion (κ = 0.8697, 95% CI = 0.6951-1) and bone reaction (κ = 0.911, 95% CI = 0.7918-1), and perfect (κ = 1) for bone, subperiostal and epiphyseal cartilage abscesses.

Bone reaction, was less frequent in patients with *K. kingae* OAI (P = 0.0066). In the *K. kingae* group, bone reaction was present in 11/21 (48%), whereas it was present in all children in the GPC group. Bone reaction was scored as slight in three children, moderate in one and severe in six (all had bone abscess). Soft tissue reaction was less severe in the *K. kingae* group (P = 0.0087). Only 4/21 (19%) with *K. kingae* presented severe soft tissue reaction compared with 8/10 (80%) in the GPC group. Moderate soft tissue reaction was present in 9/21 (43%) with *K. kingae*, mild reaction was found in seven children, and one had no soft tissue involvement at all. Epiphyseal (or equivalent) cartilage involvement with abscess formation was seen in 10/21 (48%) in the *K. kingae* group but in none within the GPC group (P = 0.0118; Figs. 1 and 2). Three children (one with *K. kingae* and two with GPC OAI) had epiphyseal involvement without abscess formation. They were all younger than 18 months and had absent enhancement of the cartilaginous epiphysis of the affected side (Fig. 3). Three in the *K. kingae* group had subperiosteal ascesses and six had bone abscesses. In the GPC group, two had subperiosteal abscess and none had a bone abscess, but this was not significantly different (P = 1 and P = 0.1411). No difference was found for joint effusion (P = 0.4414).

Using cartilaginous abscess and/or mild bone reaction (score 0-1) as diagnostic criteria for *K. kingae* gave a sensitivity of 95% and specificity of 60%. Including the absence of severe (score 3) soft tissue reaction, the specificity became 90% and sensitivity 76% with positive predictive value of 0.82 and negative predictive value of 0.75, based on the same criteria.

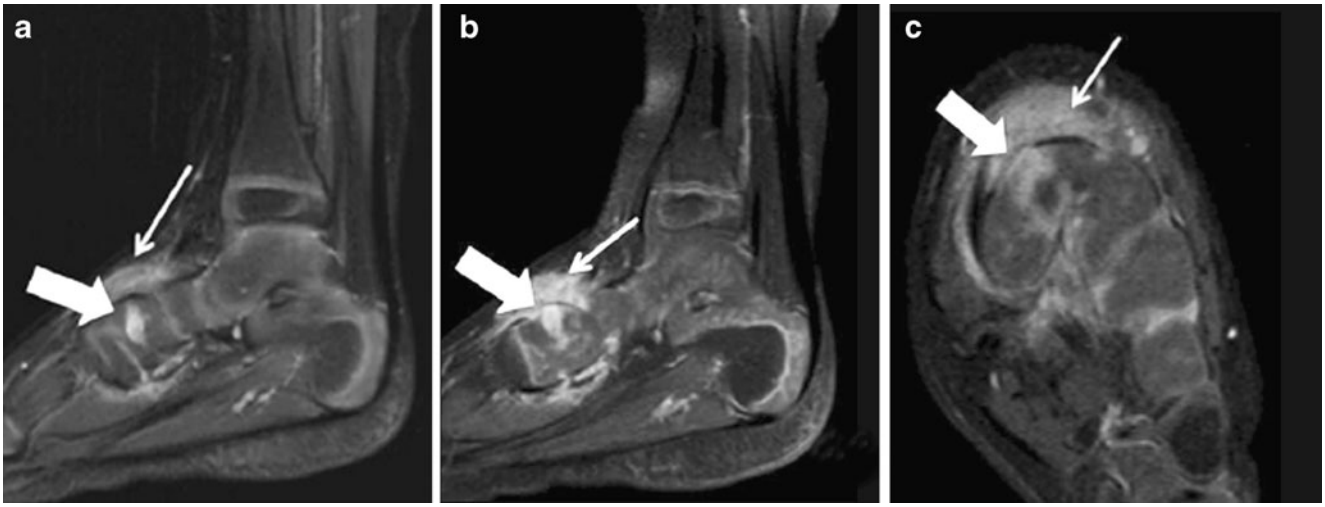

Fig. 1 A 22-month-old girl with *K. kingae* OAI of the left foot with a cartilaginous lesion in the first cuneiform bone (*thick arrow*) and moderate to severe soft tissue reaction (*thin arrow*). **a** Three-dimensional inversion recovery T2-weighted sagittal image. **b** Sagittal gadolinium-enhanced sagittal fat-saturated T1-weighted image. **c** Transaxial gadolinium-enhanced fat-saturated T1-weighted image

Discussion

In our group of 31 children with OAI and a confirmed bacteriological diagnosis, 21 (68%) were positive for *K. kingae* and only 10 (32%) were positive for GPC OAI. This is in agreement with recent literature reporting that *K. kingae* should be considered the most frequent cause of OAI in children under 4 years old [6, 16, 18, 30] in developed countries.

Invasive infections in young children are frequently caused by organisms carried asymptomatically in the respiratory tract [31]. The prevalence of *K. kingae* colonisation is higher among 6-month-old to 3-year-old children than among older children, and there is a significant decrease with age [31]. Similarly, the frequency of invasive infection is higher before the age of 4 years and decreases dramatically after this age. *K. kingae* is currently recognised to account for 5–29% of all culture-positive OAI and for up to 50% of cases of septic arthritis in children younger than 2 years of age [16]. In our practice, we have not seen child older than 4 years with *K. kingae* OAI.

In our study, the presence of joint effusion, bone abscess and subperiosteal abscess was not useful for differentiating

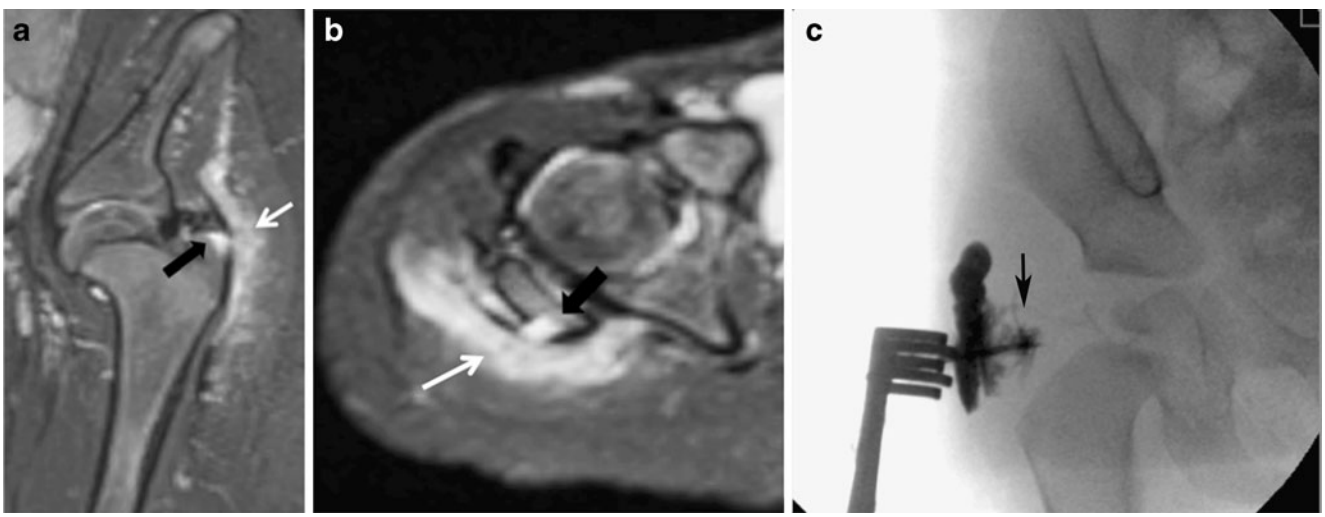

Fig. 2 An 18-month-old boy with *K. kingae* OAI of the right hip. **a**, **b** Cartilaginous lesion in the greater trochanter (*black arrow*) and moderate soft tissue reaction (*white arrow*) demonstrate on sagittal (**a**) and transaxial (**b**) 3-D inversion recovery T2-weighted images. **c** Intra-operative contrast study demonstrates the abscess in the greater trochanter (*black arrow*)

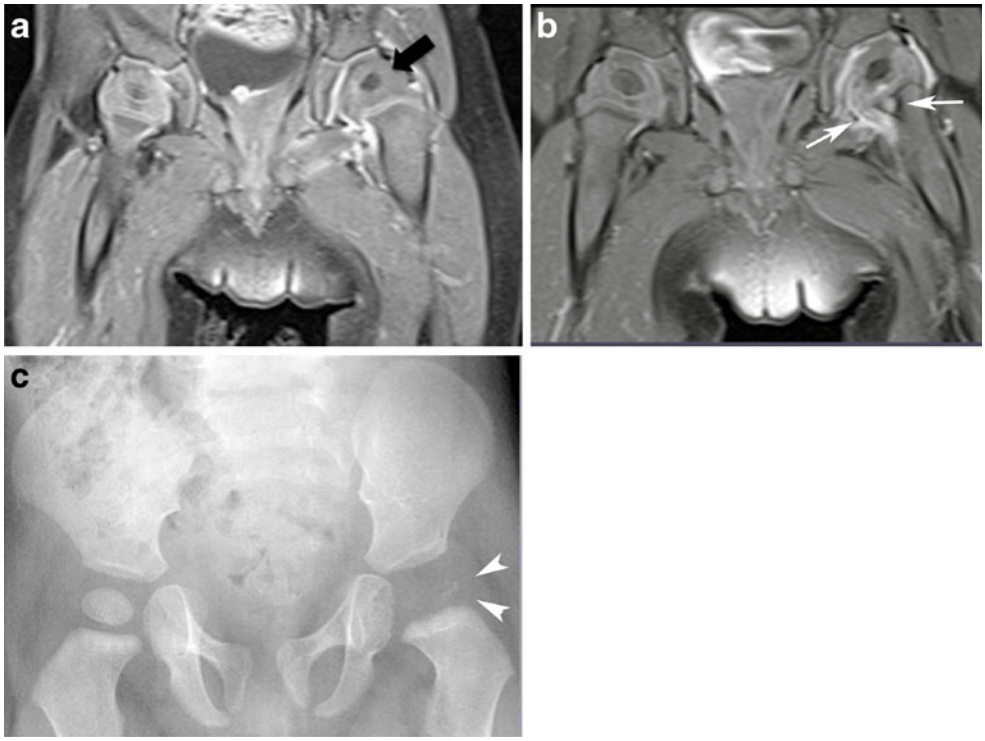

Fig. 3 A 20-month-old with OAI of the left hip caused by GPC. **a** Contrast-enhanced T1-weighted fat-saturated coronal image shows lack of enhancement of the left femoral capital epiphysis (*black arrow*). **b** Repeat MRI after 2 months shows a transphyseal abscess (*white arrows*) and persistent absence of enhancement of the epiphyseal ossification centre. **c** Radiography confirms destruction of the left femoral capital ossification centre (*arrowheads*)

causative organisms. The non-significance may be due to the relatively small sample size.

Bone involvement was less frequent (about 50%) and soft tissue reaction milder in children with *K. kingae* OAI. Bone involvement was present in all the children in the GPC group. Fewer than 20% of *K. kingae* OAIs presented severe soft tissue reaction compared with 80% of GPC OAIs. These findings are probably related to the milder clinical course of *K. kingae* OAI compared with OAI due to pyogenic microorganisms.

We also noticed that children with *K. kingae* OAI demonstrated a strikingly high frequency of epiphyseal cartilage lesions compared with those with GPC OAI.

More precisely, children in the *K. kingae* group presented localised epiphyseal cartilaginous lesions, hyperintenses on T2-weighted images and hypointenses on T1-weighted images, with peripheral enhancement. This type of lesion was never found in the GPC group. This may be related to a different pathophysiologic mechanism, which remains to be investigated.

Two children in the GPC group and one in the *K. kingae* group presented a significant lack of contrast enhancement of the affected epiphyseal cartilage compared with the contralateral side (epiphyseal hypoperfusion). This has been suggested to be a sign of septic arthritis and it has recently been also reported as a sign of epiphyseal osteomyelitis in pre-school age children [32, 33].

We considered osteoarticular infection as a complex including both osteomyelitis and septic arthritis. Especially in young children, septic arthritis is very often associated with bone involvement due to metaphyses being intracapsular at this age. Moreover, functional impairment can be as severe in septic arthritis as in osteomyelitis. One example of this is shown on Fig. 3. In this child, a very small intra-articular effusion, synovial enhancement and absence of epiphyseal enhancement at presentation were interpreted as signs of septic arthritis. Two months later, an MRI performed because of unfavourable evolution showed a transphyseal abscess and persistent absence of enhancement of the epiphyseal ossification centre. Follow-up radiographs showed destruction of the ossification centre.

The good positive predictive value (0.82) and negative predictive value (0.75) of MRI for the diagnosis of *K. kingae* in children with OAI suggest that the overall accuracy of MRI in discriminating *K. kingae* from GPC OAI may be considered good.

A limitation of our study is that the sample is relatively small. A second limitation is the variable anatomical location (different joint sizes), making comparisons and objective point-scale difficult to establish, and also causing difficulties in defining reproducible diagnostic criteria. The four-point scale seemed to

be a reliable tool for the evaluation of bone and soft tissue reactions in a setting were quantitative comparisons would be difficult.

Conclusion

K. kingae plays a recently recognised role in paediatric OAI: It should be included in the differential diagnosis of causative organisms in children younger than 4 years of age with mild-to-moderate clinical and biological inflammatory response. MRI is frequently performed before bacteriological results become available. In our study, the overall accuracy of MRI in discriminating *K. kingae* from GPC was high. Mild soft tissue reaction, absence or mild bone reaction and epiphyseal cartilage involvement were findings suggesting *K. kingae* rather than GPC. Image-based diagnosis may be a useful complementary tool in differentiating OAI caused by *K. kingae* from OAI caused by more aggressive organism. MRI findings suggestive of *K. kingae* may prompt the use of PCR for final diagnosis.

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