Published in final edited form as:
BMJ Case Rep. ; 2014: . doi:10.1136/bcr-2014-204544.

Fluoroquinolone Use in a Child Associated with Development of Osteochondritis Dissecans

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SUMMARY

Several etiological theories have been proposed for the development of osteochondritis dissecans. Cartilage toxicity after fluoroquinolone use has been well documented in vitro. We present a case report of a 10-year-old child who underwent a prolonged 18-month course of ciprofloxacin therapy for chronic urinary tract infections. This patient later developed an osteochondritis dissecans lesion of the medial femoral condyle. We hypothesize that the fluoroquinolone therapy disrupted normal endochondral ossification, resulting in development of osteochondritis dissecans. The etiology of osteochondritis dissecans is still unclear, and this case describes an association between fluoroquinolone use and osteochondritis dissecans development.

Keywords

Paediatrics (drugs and medicines); Drugs and medicines; Musculoskeletal and joint disorders; Drugs and medicines

BACKGROUND

Osteochondritis dissecans (OCD) is a focal, idiopathic alteration of subchondral bone structure with a risk of instability and disruption of adjacent articular cartilage that may result in premature osteoarthritis. OCD is more common in males, and has been found to have the greatest incidence in patients between the ages of 10 and 20.[1] Factors that predispose individuals to OCD include ischemia, [2-4] heredity, [5-9] trauma, and either acute or repetitive microtrauma.[4,10-17] The etiology of this disorder is still unclear, and may be multifactorial.

Fluoroquinolones (e.g. ciprofloxacin) are broad-spectrum antibiotics that are effective in treating both Gram negative and Gram positive bacterial infections. They are rarely used in children due to possible cartilage toxicity. While cartilage toxicity has been well documented in animal studies, recent case reports and systematic reviews also demonstrated

chondrotoxic effects with fluoroquinolone use in children.[18,19] Musculoskeletal adverse effects of fluoroquinolones include complications that impact tendon, cartilage, bone, and muscle. Most complications have been described primarily in adults, with less information available for children. Tendonopathy is a widely recognized adverse effect, with increased risk of tendonitis and tendon rupture.[20] While the Achilles tendon is commonly involved, adverse effects in several other tendons have been reported.[21,22] Arthralgia and myalgia also occur at a higher incidence in patients taking fluoroquinolones.[19,23,24] Studies examining the association between fluoroquinolones and arthropathy in children by MRI have identified cartilage abnormalities.[24] A variety of muscle-specific adverse effects have been reported ranging from myalgia to rhabdomyolysis.[23,25] Adefurin and colleagues identified numerous cases of arthralgia in children taking ciprofloxacin.[18]

The usage of ciprofloxacin is limited in the paediatric patient population because of the risk for potential adverse effects. The concern stems from studies demonstrating chondrotoxicity and irreversible cartilage damage in growing immature animals.[26,27] Further studies have demonstrated that ciprofloxacin can inhibit cell proliferation of chondrocytes and osteoblasts, as well as osteoblast differentiation and mineralization.[26,28] A study on the effects of ciprofloxacin during bone fracture healing demonstrated inefficient conversion of cartilage to bone, resulting in decreased mechanical strength of the fracture callus.[29,30] Similarities exist between the cellular mechanism of bone remodeling that occurs in the fracture callus and that which occurs at the growth plate in maturing bones. Formal studies have not been carried out on the association between ciprofloxacin and resulting adverse effects to cartilage and bone in humans and therefore little is known regarding true risk. Studies carried out in growing animals have not been consistent or conclusive, and have given rise to an ongoing debate on the usage of ciprofloxacin and other fluoroquinolones in paediatric patients.

This brief report presents a case of OCD development in a child with a history of ciprofloxacin treatment and discusses the implications of fluoroquinolone use. We are not aware of any previous description of OCD in adults or children with the use of ciprofloxacin. The authors have obtained informed written consent for print and electronic publication of this case report.

CASE PRESENTATION

A 10-year-old female patient presented to our clinic with one-month history of knee pain. She did not have a history of significant injury to her knee, but had a minor injury to her left knee one month earlier. She did not show or develop signs of swelling or limping after this minor injury. She was a relatively inactive child, with only minor participation in recreational dance. There was no family history of cartilage conditions or OCD.

Her past medical history revealed chronic urinary tract infections that were resistant to common antibiotic therapies, but were sensitive to ciprofloxacin. Under the direction of a paediatric infectious disease specialist, she was put on ciprofloxacin, 10 mg/kg for approximately 18 months between the ages of five and seven. At the time of this intervention, the specialist spoke with family about the risks, benefits, and alternatives to

using ciprofloxacin in children. The family was aware of the potential risks, and consented to proceed with the use of this medication. The patient was not on any other routine medication at the time. The British National Formulary for Children recommends a dose of 10 mg/kg by mouth twice daily for complicated urinary-tract infections in children 1 month to 18 years of age. In the case of severe infection, this dose may be doubled.[31] Prior to the start of ciprofloxacin therapy, neither the patient nor her mother reported any symptoms relating to the girl's knee.

Radiographs demonstrated subtle subchondral bone changes (Fig.1A), and an MRI of the left knee showed a stable OCD lesion of the medial femoral condyle (Fig. 1B), compared to her 3-year follow up, which showed almost complete resolution (Fig. 1C). The OCD lesion appeared to be due to a chronic injury, and there were no signs that an acute or traumatic event occurred. Her activity was restricted, and one year after her visit she remained symptomatic. An MRI at this time showed a distinct lesion without evidence of significant progression towards healing. The patient underwent knee arthroscopy for subchondral bone drilling of her medial femoral condyle OCD (Fig. 2A-B). At her 3-year follow-up, her knee function was normal, and her pain was completely resolved.

TREATMENT

The patient underwent knee arthroscopy for subchondral bone drilling of her medial femoral condyle OCD (Fig. 2A-B).

OUTCOME AND FOLLOW-UP

At her 3-year follow-up, her knee function was normal, and her pain was completely resolved. An MRI showed almost complete resolution of the lesion (Fig. 1C).

DISCUSSION

We report that an OCD lesion developed after a course of ciprofloxacin therapy in a young girl. This patient was at very low risk for developing OCD, due to an absence of regular or excessive sports activity, age, and gender. Physiologically, during development, the long bone skeleton forms initially from cartilage which then calcifies into bone during endochondral ossification. Ciprofloxacin has deleterious effects on cartilage, suggesting that long-term use of this antibiotic may have had an impact on endochondral development and the subsequent formation of subchondral bone.

Fluoroquinolone chondrotoxicity has been investigated extensively using murine and canine models.[32-34] Fluoroquinolones decrease proliferation of chondrocytes, and damage cartilage by decreasing magnesium concentrations by forming quinolone-magnesium complexes.[32,33] However, rats that ate diets supplemented with magnesium and vitamin E mitigated the cellular damage, but there was no effect on the reduction in cell proliferation.[33] The adverse effects of fluoroquinolones were further demonstrated in reports of decreased healing in the early stages of fracture repair.[29,30] Conversely, nonmurine models using lambs and chickens have not reported fluoroquinolone toxicity.[35,36] In humans, there is evidence in vivo and in vitro that links fluoroquinolone use and onset of

OCD. A recent systematic review by Adefurin and colleagues [18] analyzed 105 studies of ciprofloxacin use in children. This review reported a total of 1,065 adverse events, in which 24.2% were musculoskeletal and 12.2% had arthralgia. All musculoskeletal adverse events resolved after discontinuing fluoroquinolone treatment. These reports focused on adverse events that developed early on in the course of treatment. In vitro, fluoroquinolone treatment resulted in chondrotoxic effects and decreased cell proliferation in human chondrocyte cultures.[26-28,37] In addition, analysis of OCD lesion biopsies showed an abnormal accumulation of matrix proteins in distended, dilated, rough endoplasmic reticulum.[38] A review of the safety of prolonged (30 days to 12 months) therapy with ciprofloxacin in adults (mean of 46 years of age) identified arthralgia among symptoms due to ciprofloxacin.[39] Taken together, it is possible that prolonged use of fluoroquinolones could result in an OCD lesion formation by affecting secretory proteins that pass through the rough endoplasmic reticulum in chondrocytes. This could subsequently alter the normal development of cartilage and bone during endochondral ossification by inducing an unfolded protein response or causing a depletion in the normal matrix proteins. Further research is required to clarify the possible relationship between fluoroquinolone use and OCD lesion formation, and identify if one location in the body (e.g. femoral condyle of the femur) is more susceptible to this cellular disruption than other locations in the body.

In the case presented in this report, the use of ciprofloxacin over a prolonged period may have affected the development of the distal femur, leading to OCD. The detection of the OCD lesion occurred 3 years after the patient had completed an 18-month course of treatment with ciprofloxacin, suggesting that longer-term follow-up may be necessary to detect this side effect. Future research is needed to understand and possibly confirm the cellular and molecular basis of this clinical observation.

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LEARNING POINTS/TAKE HOME MESSAGES

-- There may be an association between fluoroquinolone use and osteochondritis dissecans development.

-- The etiology of osteochondritis dissecans is still unclear.

-- The potential for cartilage toxicity should be considered in children and a longer-term followup may be necessary to detect side effects.

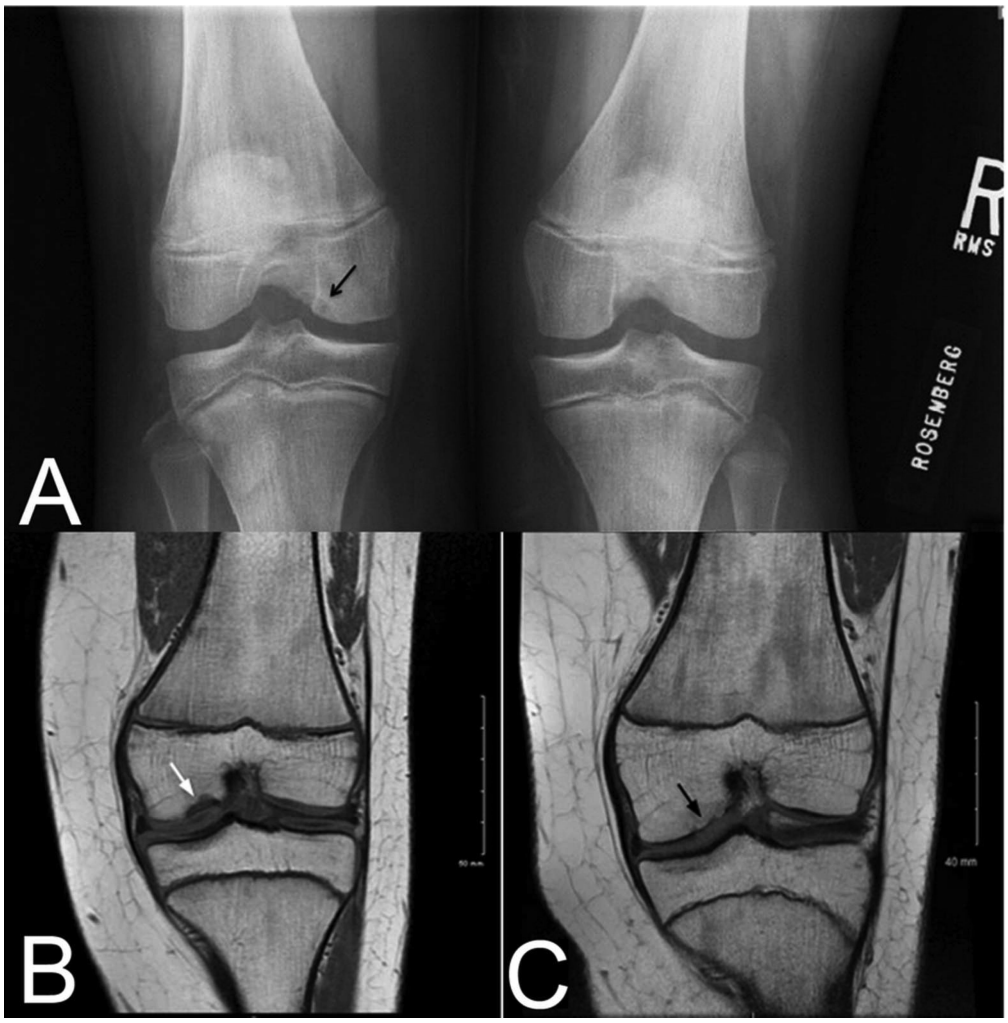

Figure 1.

Radiographic and MRI images of OCD lesion after prolonged exposure to ciprofloxacin. A. Bilateral knee radiograph. Black arrow demonstrates a stable medial femoral condyle OCD. B-C. Coronal T1 MRI sequences. Image B demonstrates a medial femoral condyle lesion (white arrow) consistent with OCD. Image C was taken at 3-year follow-up and shows good healing of OCD lesion (black arrow).

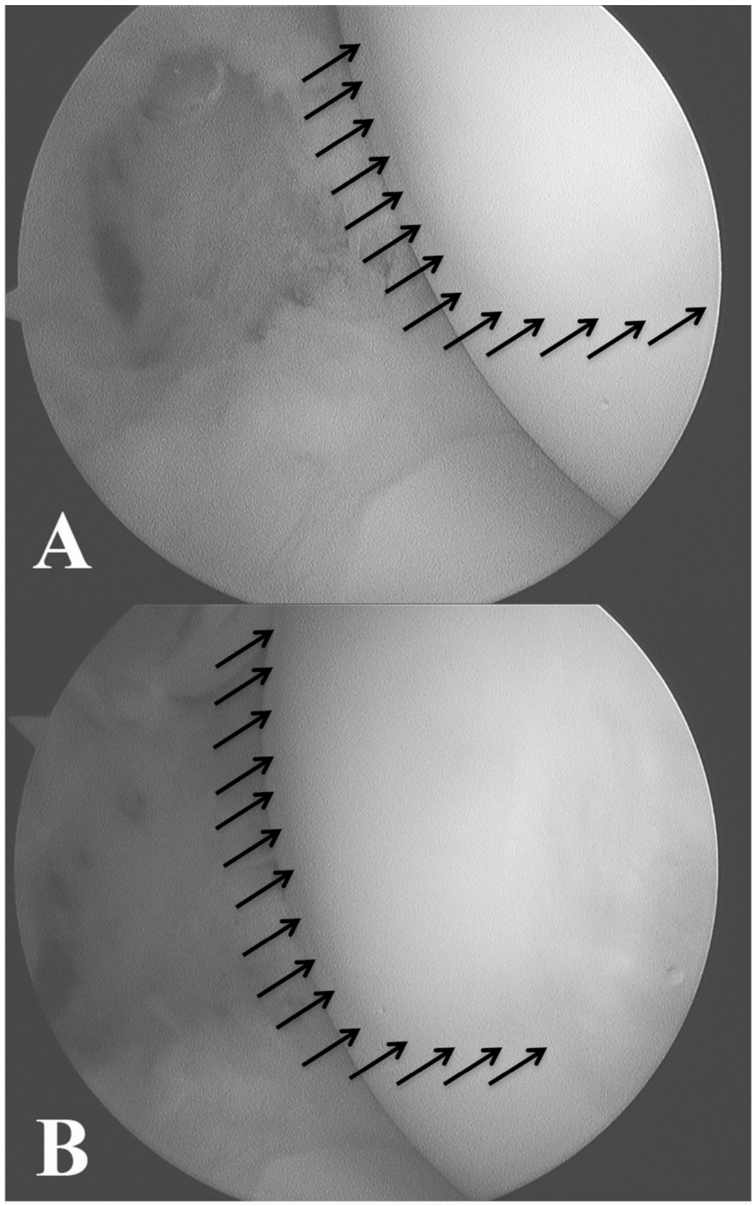

Figure 2.

Arthroscopic images of OCD lesion. Images A and B show the OCD lesion as visualized during arthroscopic surgery. The lesion demonstrates intact articular cartilage, with a slight change in the contour and color of the articular cartilage. The black arrows outline these changes.