Disturbed remodeling and delayed fracture healing in pediatric pycnodysostosis patients

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ABSTRACT

Pycnodysostosis is an autosomal recessive disease caused by a gene mutation leading cathepsin K deficiency. Pathological fractures of the long bones are common, but guidelines on fracture treatment in these patients are still lacking. We have treated 5 fractures in 2 pediatric pycnodysostosis patients. We hypothesize that pycnodysostosis patients have an incomplete remodeling process in fracture healing because of cathepsin K deficiency. Therefore, to minimize the role of endochondral bone formation (indirect) after a fracture, it seems prudent to strive for direct bone healing (intramembranous) instead of indirect bone healing. Open reduction with internal fixation should be the goal.

1. Introduction

Pycnodysostosis, also known as the Toulouse-Lautrec syndrome, is a very rare hereditary autosomal recessive lysosomal storage disease causing skeletal dysplasia.[1,2] To date, less than 200 cases have been reported worldwide.[3] It is named after Henri de Toulouse-Lautrec (1864–1901), a famous French artist of the late 19th century, who suffered from a mysterious disease. Born from consanguineous parents, he inherited a genetic disorder that left him short statured and visibly deformed.[4,5] After his death, there was much debate about his underlying disease. From the surviving documents and his self-portraits, the French doctors Mareteux and Lamy were the first to describe and diagnose him with pycnodysostosis in 1962.[6] The term pycnodysostosis is derived from Greek (*pycno* means dense, *dys* refers to defect and *osteosis* means bone pathology) and is characterized by short stature, acroosteolysis of the distal phalanges, craniofacial deformity with absence of knitting fontanels and increased bone density and fragility.[6,7]

The underlying etiology of pycnodysostosis is cathepsin K deficiency caused by a mutation in chromosome 1q21. Cathepsin K is an important enzyme produced locally by osteoclasts. It is responsible for the degradation of collagen type I which constitutes 95% of organic bone matrix.[8] The skeleton is characterized by dense bone with thick cortices, resembling osteopetrosis.[9] Despite the high density of the bone, the long bones are brittle and minimal trauma can lead to fracture.[7,9,10]

Given the rarity of the disease, guidelines on fracture treatment in pycnodysostosis are lacking. So far, only a few case reports have been reported (Table 1). We present five new fracture cases in two pediatric pycnodysostosis patients. Both had bilateral fractures of the femur. One of these patients also sustained a tibia fracture. In each patient, one femur fracture was initially treated with external fixation. After healing, the external fixator was removed. However, in both instances the femur refractured at the same location. Interestingly, histology of bone tissue from both the patients showed areas of endochondral ossification suggesting incomplete healing. Both refractures were subsequently treated with rigid internal plate fixation that led to uneventful healing. The other two femoral shaft fractures were treated with rigid internal plate fixation and healed without events. The tibia fracture was initially treated conservatively with 6 weeks of cast immobilization as it was a non-displaced fracture. After callus formation was observed on radiographs and there was no pain, a Sarmiento brace was given for another 6 weeks. However, 1 year later he refractured his tibia at the exact same location, which then required rigid internal fixation that healed uneventfully.

Our hypothesis is that external fixation or casting of long bone fractures in patients with pycnodysostosis leads to a suboptimal or delayed fracture healing, because targeted remodeling is diminished due to dysfunction of osteoclasts. To maximize the healing potential, we suggest open reduction with internal fixation in the fracture management in these patients, as this leads more likely to direct intramembranous bone healing, which does not rely on osteoclastic

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Table 1
Previous reports of pediatric pycnodysostosis patients with femur fractures.

Patient	Fracture location	Trauma	Treatment	Complication	Reference
Girl, 9 yo	Diaphyseal (bilateral)	Fall off bike	Closed reduction and fixation with MIPO	None	Rojas et al.[20]
Girl, 12 yo	Diaphyseal	Fall of trampoline	Closed reduction and fixation with MIPO	Breakage of drilling instruments, however, uneventful recovery	Matar and James[21]
Boy, 6 yo	Diaphyseal	Fall from 4 ft.	Wrist external fixation device	None	Jiya et al.[11]
Boy, 15 yo	Diaphyseal	NA	Skeletal traction and Thomas splint	None	Singh and Sambandam[22]

yo: years old; MIPO: Minimally invasive plate osteosynthesis; NA: not available.

remodeling.

2. Materials and methods

The parents and guardians of our patients have provided written informed consent for use of their medical information to be published.

Bone tissue was obtained during the open reduction and internal fixation of the right midshaft tibial fracture of our patient described as case 1 and from the right midshaft femur fracture of our patient described as case 2. In addition, we analyzed callus tissue obtained from a healthy patient. The fracture of this last patient healed normally and can be presumed to be normal callus. All tissues were deemed surgical waste as they interfered with anatomic reposition and they were procured with consent of the patients and/or their parents. Hematoxylin-Eosin (H-E) stained slides from paraffin embedded tissue samples were evaluated. Immunohistochemical staining for cathepsin K (clone 3F9, Cell Marque, Rocklin, CA, USA) was performed utilizing an automated slide preparation system (Benchmark Ultra, Ventana Medical Systems, Tucson, AZ, USA). Antigen retrieval was performed with Cell Conditioning 1 (CC1) for 24 min. The concentration of the primary antibody was 1:100 with an incubation time of 32 min. The signal detection was performed with Optiview DAB IHC detection Kit (Ventana Medical Systems, Tucson, AZ, USA). A bone pathologist evaluated all slides.

3. Case 1

Our first patient was a 6-year old boy, born from consanguineous Moroccan parents. He was diagnosed with pycnodysostosis at 10 months of age and sustained multiple long bone fractures over the years (2x bilateral midshaft femur fracture, 1x clavicle fracture, 2x midshaft tibia fracture). All fractures were the result of low energy traumatic events. At the age of 6 years, he sustained a left femoral shaft fracture that was initially managed surgically with external fixation by another department in our hospital (Fig. 1A and B). The external fixator was removed after 5 months, after healing was felt to be complete (Fig. 1C). A refracture occurred at the same location 2 years later (Fig. 1D and E). He was referred to us, and treated with open reduction and internal fixation with a 4.5 Locking Compression Plate (LCP) and non-locking screws (Johnson&Johnson, DePuy/Synthes, Amersfoort, the Netherlands). Postoperative management included 6 weeks toe-touch weight-bearing. The fracture healed uneventfully within 5 months (Fig. 1F). One year later, when he was 10 years old, the patient was readmitted with a right femoral shaft fracture which was almost a mirror image of the other side (Fig. 1A supplementary material). The fracture was treated with open reduction and internal fixation with a 4.5 LCP plate and non-locking screws (Johnson&Johnson, DePuy/Synthes, Amersfoort, the Netherlands) (Fig. 1B supplementary material). Postoperative management included 6 weeks toe-touch weight-bearing. Clinical and radiographic consolidation were seen after 4 months (Fig. 1C supplementary material) and after 3 years the hardware was removed. A year later, he presented with a right tibia shaft fracture with minimal displacement and moderate level of pain. As it was non-displaced, the fracture was treated non-operatively by the pediatric orthopedic service
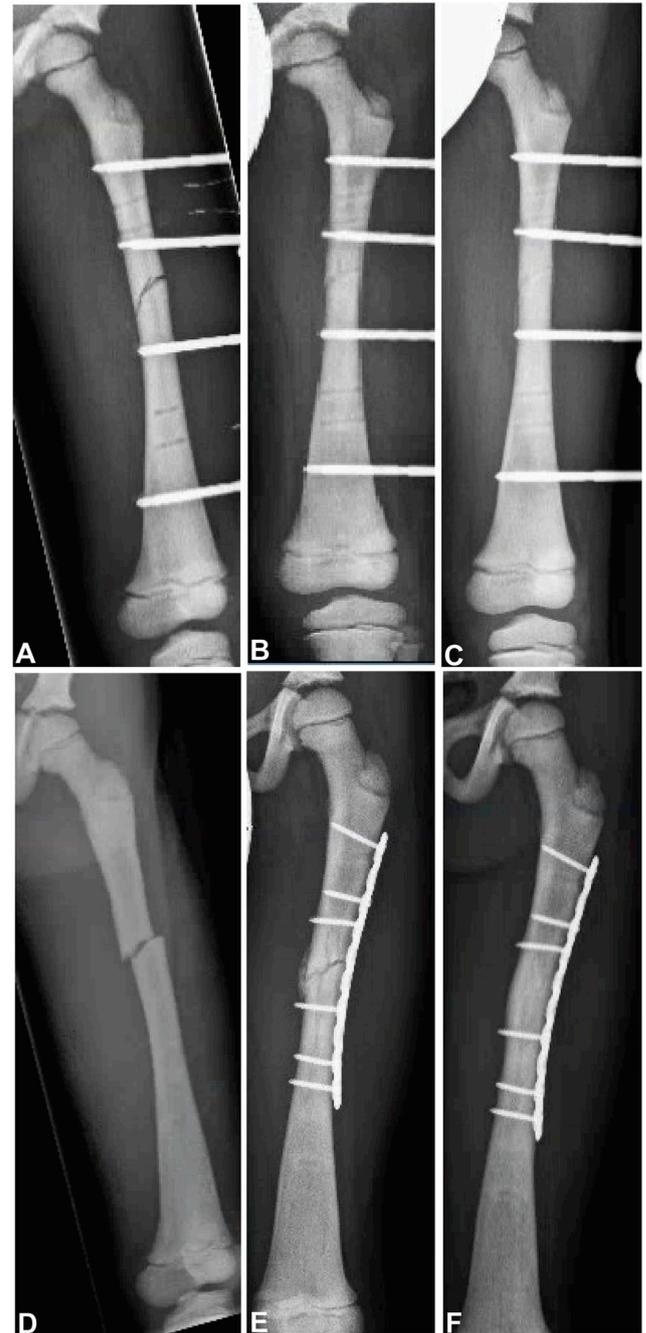

Figure 1. A. AP-radiograph showing reposition of the transverse mid-diaphyseal fracture with an external fixator. **B.** One month after surgery there are signs of consolidation. **C.** At 4 months the fracture has consolidated radiographically **D.** Two years later a refracture occurs at the same location **E.** AP-radiograph after open reduction and internal fixation. **F.** At 5 months after surgery the fracture has fully consolidated radiographically.

with 6 weeks of cast immobilization (Fig. 2A supplementary material). At 6 weeks follow-up the patient had regained full weight-bearing without pain. Radiographs showed callus formation and seemed to indicate union of the fracture (Fig. 2B supplementary material). A Sarmiento brace was given for 6 more weeks. One year later he refractured his tibia at the exact same location. Surgical treatment followed with open reduction and internal fixation with a 4.5 LCP plate and non-locking screws (Johnson&Johnson, DePuy/Synthes, Amersfoort, the Netherlands). To maximize compression the AO-tensioner device was used as in the other cases (Fig. 2C supplementary material). Post-operative management initially included 6 weeks toe-touch weight-bearing (Fig. 2D supplementary material). However, postoperatively he complained about pain in his right femur. Radiographic analysis showed that he had refractured his femur at the same location as 4 years prior (Fig. 2E supplementary material). As it was a non-displaced stress-fracture, it was treated non-operatively. The post-operative management was changed to 6 weeks of cast immobilization. At 6 months, radiographs seemed to indicate union of the femur shaft fracture and at final follow-up 8 months postoperatively, he had no complaints and complete union of the tibia shaft fracture was noted on radiographs (Fig. 2F supplementary material).

4. Case 2

The second patient was a nephew of the patient described in case 1, also born from consanguineous parents. He had already sustained fractures in both femur fractures, which were caused by minor trauma. At the age of 5 he sustained a left femur shaft fracture that was initially treated by external fixation in another hospital.[11] The external fixator was removed after 6 weeks when callus formation was noted on radiographs and the patient was ambulating without pain. When he was 11 years old, he presented with a femoral fracture on the right side (Fig. 3A supplementary material). An open reduction and internal fixation was performed with a 4.5 LCP plate and non-locking screws (Johnson&Johnson, DePuy/Synthes, Amersfoort, the Netherlands) (Fig. 3B supplementary material), which resulted in uneventful healing at 9 months postoperatively (Fig. 3C supplementary material).

Five years later, at age 16, he presented to us with a refracture of his left femoral shaft (Fig. 3D supplementary material). Open reduction and internal fixation with a 4.5 LCP plate and both locking and non-locking screws was performed (Johnson&Johnson, DePuy/Synthes, Amersfoort, the Netherlands) (Fig. 3E supplementary material). For compression across the fracture the AO tensioner device was again used. Postoperative management included 6 weeks of toe-touch weight-bearing. At 6 weeks follow-up the patient had regained full weight-bearing without pain. Radiographs showed complete union of the fracture at 12 months (Fig. 3F supplementary material).

5. Results

It is well known that cathepsin K is strongly expressed in osteoclasts.[12] It has also been demonstrated that cathepsin K is expressed in hypertrophic chondrocytes undergoing apoptosis.[13] Abundant presence of cathepsin K staining is seen in normal fracture callus tissue (Fig. 2A). As expected, there was complete absence of cathepsin K staining in the fracture tissue from both the patients with pycnodysostosis (Fig. 2B and C). Fig. 2D demonstrates a H-E staining of the fracture of a healthy patient. Areas of endochondral bone formation are seen with plump osteoblasts rimming the surface of newly formed osteoid. Interestingly, H-E staining of both the patients with pycnodysostosis show remnants of endochondral bone formation, indicating an incomplete remodeling process. Areas of newly formed osteoid tissue are seen lined by osteoblasts (Fig. 2E and F). The osteoid tissue consists of stromal tissue with herein fibroblastic cells. No osteoclasts are seen (Fig. 2E and F).

6. Conclusion and discussion

Both our patients had one of their femoral shaft fractures initially treated with external fixation. A large callus was noted on radiographs suggesting solid healing. After removal of the external fixation both patients refractured their femur at the same location after low energy trauma. This was after 1.5 years for our first patient and 11 years for our patient described as case 2. A similar outcome was seen after non-operative treatment of a midshaft tibia fracture. The initial radiographic findings in all these fractures have the appearance of a stress fracture in the lateral cortex. This is the area of the bone that is under tensile stress because of the bowing.

Based on our histology the tibia callus had not fully matured (i.e. remodeled) as there were remnants of endochondral bone formation. In our second case, the bone pathologist had mentioned remnants of endochondral bone formation or suggestion of an enchondroma. A similar pattern of endochondral bone formation is very likely to have been present after the femoral shaft fractures treated with the external fixator. We think these delayed fracture healings are caused by cathepsin K deficiency. Because cathepsin K has a key role in osteoclast-mediated bone resorption during fracture healing, it is the reduced or absent expression in osteoclasts of pycnodysostosis patients that will result in incomplete remodeling, i.e. conversion of endochondral bone (soft callus) into hard callus. It is well established that external fixation induces endochondral bone formation whereas rigid fixation leading to direct (intramembranous) bone healing.

Another mechanism for the "refracture" could be the tensile stresses on the lateral cortex that probably also caused the initial fracture. A compression plate on the (lateral) tension side is preferred for these fractures, because it not only neutralizes the tensile forces, but also minimizes fracture micromotion and converts the tensile stress into compression stress on the lateral cortex. We showed this concept of tension band plating previously in stress fractures in the tibia.[14]

While a diminished remodeling process due to dysfunctional osteoclasts and interfragmentary strain in secondary bone healing explains the inability to heal the fracture, this does not explain why the fracture occurred in the first place. Microcracks occur regularly in bones, but go unnoticed in healthy individuals because these are repaired by targeted remodeling. This is a process during which microdamage is selectively targeted by osteoclasts, resorbed and replaced by osteoblasts. In patients with pycnodysostosis this ability to remodel is limited because of dysfunctional osteoclasts. As a result, the accumulation of microdamage leads to a stress fracture. It seems prudent to treat these impending fractures before they break.

A similar pattern is seen in so-called atypical femoral shaft fractures. These atypical femoral shaft fractures are a rare type of stress fracture. The incidence is increasing and has been associated with bisphosphonate treatment. In hindsight, the transverse fractures of the femur in our pycnodysostosis patients resemble those seen in the atypical proximal femur fractures.[15,16] Bisphosphonates inhibit osteoclast activity and suppress bone turnover. This is thought to increase the risk of stress fractures and the atypical femoral shaft fractures, because of the reduced remodeling process.[17–19]

A dysfunctional osteoclast, whether by cathepsin K deficiency or by long-term bisphosphonate use may explain radiological similarities between the femoral fractures seen in both patient groups.

Despite the small number of patients in this report, we think this hypothesis is an important step in better understanding fracture healing in pycnodysostosis patients. It is unlikely that any hospital will have a large exposure these patients. As such it is difficult to provide guidelines. Based on the failure of external fixation for femoral fractures, our current protocol consists of rigid open compression plate fixation, aiming for direct bone healing. Because the diameter of the intramedullary canal is very small, there is in our opinion no role for intramedullary fixation. We propose that open reduction with rigid internal fixation should be the goal in fracture management in patients
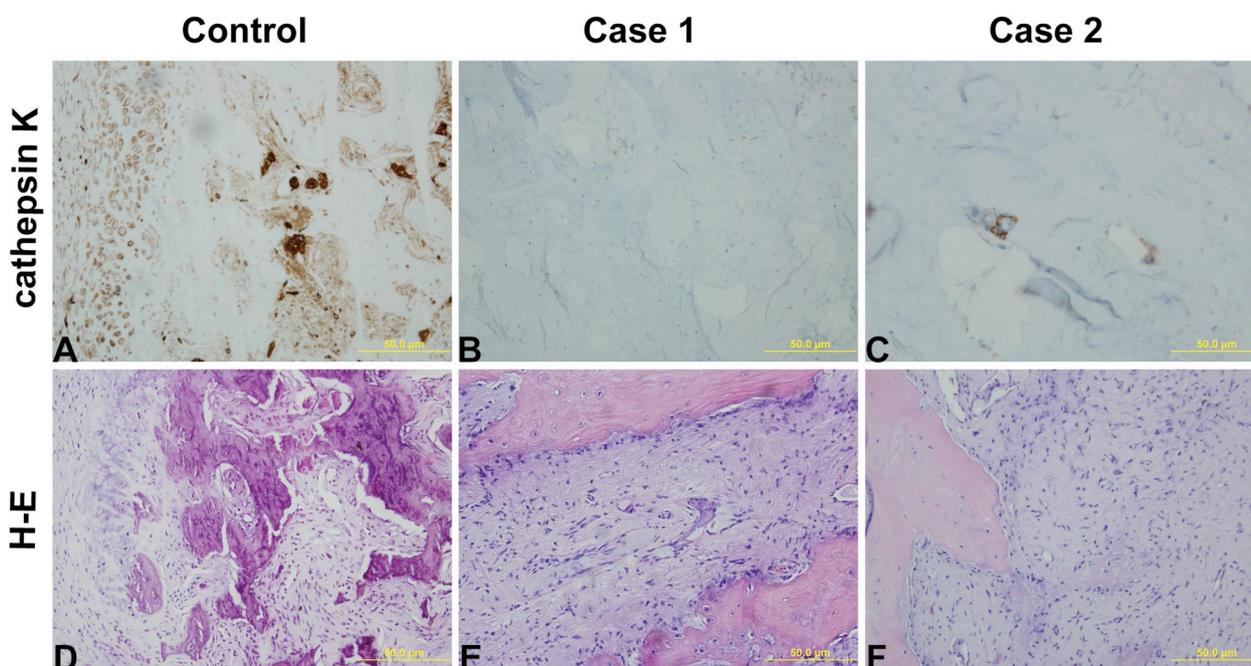
Figure 2. A. Cathepsin K staining in normal fracture callus tissue. Cathepsin K-positive staining is seen in osteoclasts and hypertrophic chondrocytes **B–C.** Complete absence of cathepsin K staining in the fracture tissue of bone from both the pycnodysostosis fracture patients, case 1 and case 2 respectively **D.** H-E staining of a fracture of a healthy patient. There are areas of endochondral bone formation with plump osteoblasts rimming the surface of newly formed osteoid. Osteoclasts and osteocytes are seen **E-F.** H-E staining of the fracture of both our pycnodysostosis patients, case 1 and case 2 respectively. Areas of newly formed osteoid tissue are seen lined by osteoblasts is seen. The osteoid tissue consists of stromal tissue with herein fibroblastic cells. No osteoclasts are seen.

with pycnodysostosis as this leads to direct (intramembranous) bone healing, which is not dependent on osteoclastic remodeling. As a disturbed remodeling process and a delayed fracture healing are difficult to distinguish macroscopically, we recommend not to remove the hardware. The compression plate prevents micromotion and microcracks, which subsequently reduces the risk for a stress fracture.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of interest

Simran Grewal, Özgür Kilic, C. Dilara Savci-Heijink and Peter Kloen declare they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jor.2019.03.022.

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