# Femur fractures in 5 individuals with pantothenate kinase-associated neurodegeneration: the role of dystonia and suggested management

Laken Behrndt, MD, Allison Gregory, MD, Katrina Wakeman, BS, Alison Freed, BA, Jenny L. Wilson, MD, Robert Spaull, MBBS, Manju A. Kurian, PhD, Santosh Mordekar, MD, James A. Fernandes, MCh Orth, Susan J. Hayflick, MD, Penelope Hogarth, MD, and Scott Yang, MD

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**Abstract**

*Background:*

Pantothenate kinase-associated neurodegeneration (PKAN) is a rare, neurodegenerative disorder that manifests with progressive loss of ambulation and refractory dystonia, especially in the early-onset classic form. This leads to osteopenia and stress on long bones, which pose an increased risk of atraumatic femur fractures. The purpose of this study is to describe the unique challenges in managing femur fractures in PKAN and the effect of disease manifestations on surgical outcomes.

*Methods:*

A retrospective case review was conducted on five patients (ages 10-20 years) with PKAN with a femur fracture requiring surgical intervention. Data regarding initial presentation, surgical treatment, complications, and outcomes were obtained.

*Results:*

All patients were non-ambulatory, with four of five patients sustaining an atraumatic femur fracture in the setting of dystonia episode. One patient had an additional contralateral acetabular

fracture. Post-operatively, four of the five patients sustained orthopedic complications requiring surgical revision, with three of these secondary to dystonia. Overall, four required prolonged hospitalization in the setting of refractory dystonia.

*Conclusion:*

Femur fractures in PKAN present distinct challenges for successful outcomes. A rigid intramedullary rod with proximal and distal inter-locking screws is most protective against surgical complications associated with refractory dystonia occurring during the post-operative period. Multi-disciplinary planning for post-operative care is essential and may include aggressive sedation and pain management to decrease the risk of subsequent injuries or complications.

*Level of Evidence:*

Level IV.

## Introduction

Pantothenate kinase-associated neurodegeneration (PKAN) is a rare, autosomal recessive neurodegenerative disorder associated with abnormal iron accumulation within the brain (OMIM 234200, https://www.omim.org/entry/234200). Classic disease presents in early childhood (age <6 years) while atypical cases may present beyond the first decade of life.[1] PKAN is associated with progressive, severe dystonia which results in progressive loss of independent motor function and medical complications. The clinical diagnosis is supported by iron-sensitive sequences on brain MRI, with axial $T_2$-weighted imaging demonstrating central hyperintensity of the globus pallidus with a surrounding region of hypointensity (the pathognomonic "eye of the tiger" sign). Genetic testing with identification of two pathogenic or likely pathogenic *PANK2* variants confirms the diagnosis in most cases.[2]

The hallmark symptom of PKAN is generalized dystonia. The disease progresses throughout childhood and adolescence. Spasticity may also be present but does not dominate the clinical picture. As dystonia worsens, children lose voluntary motor control. Most children with classic PKAN can no longer walk by late childhood.[3] The dystonia and spasticity only respond modestly to medications and botulinum toxin injections. In rare situations more invasive treatments such as intrathecal baclofen, pallidotomy or deep brain stimulation are pursued.[4] In the classic form of the disease, the deterioration is punctuated by life-threatening episodes of severe dystonia ("dystonic storms"), which may be triggered by illness, pain, medication changes or other stressors. The priority is to treat the underlying trigger, while managing dystonia with escalation of medications and sometimes general anesthesia.[4] Life expectancy varies per individual, though is typically the second decade for classic PKAN and well into young adulthood for atypical PKAN.[5]

The decrease in weight-bearing activities compounded by nutritional deficiencies results in osteopenia and risk of fragility fracture, like individuals with cerebral palsy. However, in PKAN, the bone stress related to severe dystonia may further increase the risk of atraumatic fracture and bony injury.[3] The pain from the fracture may drive an increase in dystonia, risking additional injury.

Though atraumatic long bone injury and fracture have long been recognized in PKAN,[4] there is a paucity of literature on the orthopedic manifestations of PKAN and the role of disease manifestations on surgical complications and outcomes. This study's purpose was to describe patients with PKAN with femur fractures and to highlight the unique challenges of surgical intervention and the complex outcomes seen in PKAN in the setting of the dystonia.

## Methods

We conducted a retrospective case review across five international healthcare institutions and identified five pediatric and adolescent patients with PKAN from July 2008 to April 2022 who presented with a femur fracture requiring surgical intervention. Demographics, injury mechanisms, imaging, surgical treatments, dystonia management, complications and outcomes were abstracted from the electronic health record. Data for each patient were then summarized (Table 1) and analyzed for common patterns and themes in both initial presentation and subsequent complications as they relate to the manifestations of PKAN.

## Results

The five patients were 10 to 20 years old **(mean 13.6 years)** at the time of initial injury; four had classic disease, one had atypical disease (patient D). Mean follow-up after injury was 11

months. All patients were living at home and non-ambulatory at the time of their presentation, with subjective reduced femoral cortical thickness on initial radiographic studies**.** Four of five patients were dystonic at the time of injury. Injury mechanism for each patient is detailed in Table 1. Of note, while reviewing medical records, we identified three instances of healing or healed fractures of the ribs or tibia that were identified incidentally during the evaluation for their femur fractures (patients D, B, C). The possibility of non-accidental trauma was considered in these cases but was determined to be unlikely.

All patients sustained femoral shaft fractures, with examples demonstrated in Figures 1, 2, and 3 for patients B, C, and E, respectively. Patient D also had a contralateral acetabular fracture at the time of presentation. Of the five patients who presented with a femoral shaft fracture, two underwent rigid intramedullary nail fixation via a trochanteric entry nail (patients C and D). Patient D's intramedullary nail was locked with proximal and distal inter-locking screws, while patient C's intramedullary nail was locked only with proximal inter-locking screws (Figure 2B), as there was concern for recurring dystonia and re-fracture at the interlock screw site secondary to the surgeon's subjective assessment of poor metaphyseal bone strength. A rigid intramedullary nail was considered in patient A, but two elastic nails with one each placed in anterograde and retrograde fashion supplemented with Luque wires were used, as there was not a rigid nail of appropriate dimensions available at the facility for the patient's small femoral anatomy. Two elastic nails were also used for initial fixation in patient E (Figure 3B). Patient D, who sustained a contralateral acetabular fracture, was also treated with a Girdlestone procedure to remove femoral head protrusion stress onto the acetabulum. Patient B was not treated with an intramedullary nail; rather, a submuscular plate was used with proximal and distal screws bridging the fracture (Figure 1B).

Post-operatively, four of the five patients sustained orthopedic complications requiring revision, three of which were in the setting of severe dystonia. In patient B, a periprosthetic fracture at one of the proximal screws and failure of fixation occurred after an episode of severe dystonia 2 days post-operation (Figure 1C). The submuscular plate was removed, and revision was made with a rigid intramedullary nail with proximal and distal inter-locking screws (Figure 1D). No further orthopedic complications occurred during hospitalization. In patient C, the fracture shortened over the intramedullary rod and migrated into the knee joint space following an episode of dystonia 1 week post-operation (Figure 2C). Patient C then sustained a femoral shaft fracture to the opposite leg after hitting the leg on the bedrail 2 weeks post-operation. For the initial injury with rod migration, the fracture was reduced to length over the same intramedullary nail and distal interlocking screws were added and weight-based maximum dose of botulinum toxin was injected into the left upper leg muscles to decrease the force of the dystonia (Figure 2D). After healing, they were treated with bisphosphonates and have had no further fractures, now 3 years later. For the contralateral femur fracture, a rigid intramedullary nail with both proximal and distal interlocking screws was utilized with no subsequent surgical complications. In patient E, there was failure of fixation with varus deformity following breakage of the medial elastic nail, which occurred about 1 month post-operation, in the setting of significant worsened generalized dystonia (Figure 3C). The elastic nails were removed and replaced with a rigid intramedullary nail with proximal and distal inter-locking screws (Figure 3D). The fracture remained stable at 2- and 6-month follow-ups with no evidence of failure. In patient A, there was migration of the proximal antegrade elastic nail leading to exposed hardware approximately 5 weeks post-operation. This nail was removed, and the distal retrograde elastic

nail was shortened and angled to prevent further migration, while supplementing the remainder of the healing with immobilization in a single-leg spica cast.

Four of the five patients required hospitalization longer than 1 month in the setting of refractory dystonia. All patients were treated with multidisciplinary care teams, including neurology. Only patient A did not experience worsening post-operative dystonia and had a total length of hospitalization of 4 days for both the initial and revisional surgeries, with subsequent follow-up in the outpatient setting. The patients with refractory dystonia had a mean length of hospitalization of 9 weeks, with a range of 5 weeks to 4 months. Patient B required post-operative re-intubation due to respiratory failure, with subsequent involvement of anesthesia and neurology teams for careful post-operative weaning of sedation and drug management of dystonia. Patient D had prolonged dystonic storming greater than two months after femur fracture fixation that required propofol infusion, benzodiazepines, and phenobarbital for control, possibly due to continued pain after Girdlestone procedure**.** Patient E was hospitalized for 1 month with subsequent hospice admission. Patient E's dystonia remained severe following the initial injury, requiring subcutaneous infusions of midazolam, levomepromazine, and diamorphine for palliation. Patient E died from cardiopulmonary failure approximately 6 months after sustaining the femur fracture.

## Discussion

This case series illustrates several clinical features intrinsic to PKAN that may predispose this population to atraumatic femur fractures and a complicated post-operative course. In all cases, the injuries occurred in non-ambulatory patients with advanced disease. The loss of weight-bearing abilities increases the risk for osteopenia, a feature suspected in all patients in

this study. This, in turn, increases the risk of fractures. Thus, it is imperative for patients with PKAN to be monitored closely for signs of new atraumatic orthopedic injury as their disease progresses.

Illustrative of this, in three patients we identified evidence of previous healing or healed fractures that had not been identified at the time of injury and were instead discovered during later imaging. The PKAN consensus guidelines for bone health are informed by evidence and consensus-based cerebral palsy guidelines,[6,7] recommending appropriate intake of calcium and vitamin D, bisphosphonates in those who have had a fracture, and engagement in weight-bearing activities. Dual energy X-ray absorptiometry (DEXA) also been suggested for assessment of bone health**.** Femoral shaft fractures were also noted to occur in the setting of progressively worsening dystonia or during dystonic storming. While pain resulting from fracture or dislocation might be expected to precipitate a dystonic crisis, the temporal profile in most of our cases suggested that dystonia may have caused the injuries presumably from extreme bone stress.

*Preferred methods of fixation for fractures in PKAN*

Our review of the surgical complications suggests the most effective method of surgical stabilization of femur fractures seen in PKAN is a rigid, proximally and distally locked intramedullary nail when anatomy allows. All patients with a femoral shaft fracture treated without a rigid proximal and distal inter-locking femoral nail sustained a mechanical complication, such as rod migration, hardware failure, and periprosthetic screw fracture. Multiple studies have recommended elastic nailing as a simpler and less invasive intervention for subtrochanteric fractures in pediatric patients of low body weight.[8–10] However, in patients with

PKAN undergoing ongoing mechanical stress related to their dystonia, a more rigid locked intramedullary nail may need to be considered. Submuscular plate fixation has also been recommended as a safe and effective treatment for pediatric femoral fractures.[11,12] Despite its stability, plate fixation is speculated to increase the risk of implant-related fractures, especially in patients with osteoporosis, due to its stress-shielding effect.[13] In individuals with PKAN who already have osteopenic bone undergoing dystonic stress, the use of plate fixation could further increase their risk of atraumatic fracture.- Thus, when technically feasible, a rigid intramedullary nail with both proximal and distal inter-locking screws is the best surgical option to avoid surgical complications from recurring postoperative dystonia.

Although postoperative immobilization in a hip spica cast can be a reasonable consideration, the authors don't routinely recommend them for the following reasons: 1) the size of the patient is often a large child or early adolescent 2) Patients are very sensitive to temperature and skin discomfort which can be triggers of dystonia 3) Patients are often sedated and immobile for prolonged periods for which the development of iatrogenic pressure sores are a significant risk in the intensive care setting where staff are not used to evaluate frequently at the edges of the casts 4) The need for frequent neural axis anesthesia infusion checks if an epidural or lower extremity infusion block is placed and 5) Most patients with rigidly locked intramedullary nails in this series did not have a spica cast healed well without peri-implant complication.

*Pharmacologic management of dystonia in the post-operative setting*

Post-operatively, dystonic storming should be anticipated after a fracture in PKAN. Dystonia is worsened in setting of stress, illness, pain, abrupt medication changes, anesthesia,

and surgery, which are all standard occurrences during treatment of a fracture or dislocation. Dystonia may complicate orthopaedic care, increase pain, and cause oromandibular rigidity which can make airway maintenance a challenge.[14] Several studies have demonstrated the need for intubation to maintain the airway in PKAN patients receiving sedation.[14,15,15–17] Post-operative respiratory failure is a complication in PKAN patients that must be considered when receiving sedation, and re-intubation occurred in one of our patients, as well as in cases reported in the literature.[14]

In our case series, dystonia progression was often found to be refractory to pharmaceutical management. Even brief periods of severe dystonia may result in post-surgical complications. With a rigid locked intramedullary nail, surgical pain can be expected to be much improved after 4-7 days. However, if a rigid locked nail cannot be placed, and dystonia may complicate healing, consideration of a prolonged 3-4 week period of aggressive dystonia management may be warranted to prevent mechanical fracture fixation failure from dystonia.

Multidisciplinary teams should establish a plan for sedation, pain and dystonia management (Figure 4). One approach is to plan for a period of intubation and sedation, although in some patients this may be "lifted" early if they are doing well. However, there may be some children with PKAN who are less susceptible to status dystonicus and may not require this. An epidural catheter and/or nerve block may be considered as tools for pain control. The pharmacologic approach in this setting is a rapid introduction or increase in medications, often including rapidly titratable infusions (e.g. midazolam) under the care of an intensivist and movement disorder specialist. Non-pharmacologic approaches to decrease dystonia may include use of a fan, playing a favorite movie, or treating anxiety.[18]

## Conclusion

This is the first case series to report on atraumatic orthopedic injuries in PKAN. Osteopenia and severe dystonia may be risk factors for atraumatic orthopedic injury in this population. Furthermore, recurrent, refractory dystonia during the post-operative period increases the risk of post-operative orthopedic complications and prolonged hospitalization. Rigid intramedullary nail with proximal and distal inter-locking screws is suggested as the preferred fixation for femoral fractures, to minimize the risk of complications requiring surgical revision. Finally, optimal anesthesia and pharmacological management during the peri-operative and post-operative period are paramount in controlling dystonia and protecting against complex orthopedic complications.

1. Hayflick SJ, Westaway SK, Levinson B, et al. Genetic, clinical, and radiographic delineation of Hallervorden-Spatz syndrome. *N Engl J Med*. 2003;348(1):33-40. doi:10.1056/NEJMoa020817

2. Hogarth P. Neurodegeneration with brain iron accumulation: diagnosis and management. *J Mov Disord*. 2015;8(1):1-13. doi:10.14802/jmd.14034

3. Gregory A, Hayflick SJ. Pantothenate Kinase-Associated Neurodegeneration. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews®*. University of Washington, Seattle; 1993. Accessed September 6, 2023. http://www.ncbi.nlm.nih.gov/books/NBK1490/

4. Hogarth P, Kurian MA, Gregory A, et al. Consensus clinical management guideline for pantothenate kinase-associated neurodegeneration (PKAN). *Mol Genet Metab*. 2017;120(3):278-287. doi:10.1016/j.ymgme.2016.11.004

5. Natural history and genotype-phenotype correlation of pantothenate kinase-associated neurodegeneration - Chang - 2020 - CNS Neuroscience & Therapeutics - Wiley Online Library. Accessed September 6, 2023. https://onlinelibrary.wiley.com/doi/10.1111/cns.13294

6. Informing evidence-based clinical practice guidelines for children with cerebral palsy at risk of osteoporosis: an update - PubMed. Accessed September 6, 2023. https://pubmed.ncbi.nlm.nih.gov/27435427/

7. Osteoporosis in Cerebral Palsy | AACPDM. American Academy for Cerebral Palsy and Developmental Medicine. Accessed September 6, 2023. https://www.aacpdm.org/

8. Basa CD, Kacmaz IE, Zhamilov V, Reisoglu A, Agus H. Can titanium elastic nail be safely used for paediatric subtrochanteric femur fractures? *J Pediatr Orthop B*. 2021;30(1):1-5. doi:10.1097/BPB.0000000000000766

9. Pombo MW, Shilt JS. The definition and treatment of pediatric subtrochanteric femur fractures with titanium elastic nails. *J Pediatr Orthop*. 2006;26(3):364-370. doi:10.1097/01.bpo.0000203005.50906.41

10. Xu Y, Bian J, Shen K, Xue B. Titanium elastic nailing versus locking compression plating in school-aged pediatric subtrochanteric femur fractures. *Medicine (Baltimore)*. 2018;97(29):e11568. doi:10.1097/MD.0000000000011568

11. Hedequist D, Bishop J, Hresko T. Locking plate fixation for pediatric femur fractures. *J Pediatr Orthop*. 2008;28(1):6-9. doi:10.1097/bpo.0b013e31815ff301

12. Eidelman M, Ghrayeb N, Katzman A, Keren Y. Submuscular plating of femoral fractures in children: the importance of anatomic plate precontouring. *J Pediatr Orthop B*. 2010;19(5):424-427. doi:10.1097/BPB.0b013e32833c665e

13. Chung MK, Kwon SS, Cho BC, et al. Incidence and risk factors of hardware-related complications after proximal femoral osteotomy in children and adolescents. *J Pediatr Orthop B*. 2018;27(3):264-270. doi:10.1097/BPB.0000000000000448

14. Hinkelbein J, Kalenka A, Alb M. Anesthesia for patients with pantothenate-kinase-associated neurodegeneration (Hallervorden-Spatz disease) - a literature review. *Acta Neuropsychiatr*. 2006;18(3-4):168-172. doi:10.1111/j.1601-5215.2006.00144.x

15. Keegan MT, Flick RP, Matsumoto JY, Davis DH, Lanier WL. Anesthetic management for two-stage computer-assisted, stereotactic thalamotomy in a child with Hallervorden-Spatz Disease. *J Neurosurg Anesthesiol*. 2000;12(2):107-111. doi:10.1097/00008506-200004000-00006

16. Balas I, Kovacs N, Hollody K. Staged bilateral stereotactic pallidothalamotomy for life-threatening dystonia in a child with Hallervorden-Spatz disease. *Mov Disord*. 2006;21(1):82-85. doi:10.1002/mds.20655

17. Roy RC, McLain S, Wise A, Shaffner LD. Anesthetic management of a patient with Hallervorden-Spatz disease. *Anesthesiology*. 1983;58(4):382-384. doi:10.1097/00000542-198304000-00017

18. Lumsden DE, King MD, Allen NM. Status dystonicus in childhood. *Curr Opin Pediatr*. 2017;29(6):674-682. doi:10.1097/MOP.0000000000000556

## Table and Figure Legends

Table 1: Summary of data on 5 patients with PKAN presenting with femur fractures requiring surgical treatment

Figure 1: Radiographic course of submuscular plate (Patient B)

Antero-posterior and lateral radiographic imaging from patient B. This radiographic course respectively displays: (A) initial femoral shaft fracture, (B) initial surgical treatment, (C) fixation failure after dystonic episode, (D) surgical revision

Figure 2: Radiographic course of proximally-locked rigid intramedullary nail (Patient C)

Antero-posterior and lateral radiographic imaging from patient C. This radiographic course respectively displays: (A) initial femoral shaft fracture, (B) initial surgical treatment, (C) Intramedullary nail migration after dystonic episode, (D) surgical revision with adequate alignment and healing

Figure 3: radiographic course of elastic nails (Patient E)

Antero-posterior and lateral radiographic imaging from patient E. This radiographic course respectively displays: (A) initial femoral shaft fracture, (B) initial surgical treatment, (C) fixation failure after dystonic episode, (D) surgical revision with adequate alignment and healing

Figure 4: Guidelines for managing dystonia in patients with PKAN in the setting of femur fractures

Fracture in children with PKAN may be caused by and precipitate a dystonic storm. The pain from the fracture exacerbates dystonia and leads to further orthopedic complications. The lower boxes describe the approaches that allow for fracture healing by preventing and treating dystonia. The upper boxes describe primary and secondary

fracture prevention recommendations and screening. A multidisciplinary team should create a plan which may include some of these medications/measures.

*Bisphosphonates are recommended for secondary prevention of fracture

**Caution should be used with proprofol in children due to risk of propofol-related infusion syndrome