

Pycnodysostosis with Multi-Segmental Spinal Canal Stenosis due to Ossification of the Yellow Ligament

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Pycnodysostosis is an autosomal recessive disorder characterized by osteosclerosis, small stature, acro-osteolysis of the distal phalanges, loss of the mandibular angle, separated cranial sutures with open fontanels, and frequent fractures. One identified cause of the disease is reduced activity of the cysteine protease cathepsin K. A 48-year-old woman with a history of frequent fractures presented with a severe gait disturbance. Radiography, computed tomography, magnetic resonance imaging, and gene analysis were performed. Physical examination revealed open fontanels, and radiographs showed increased bone density. DNA sequence analysis revealed a deletion mutation of the cathepsin K gene. We diagnosed pycnodysostosis based on these findings. The magnetic resonance and computed tomography images demonstrated multilevel spinal canal stenosis due to ossification of the yellow ligament. We performed a laminectomy, and the patient's neurological signs and symptoms improved. To our knowledge, this is the first case of pycnodysostosis with ossification of the yellow ligament.

Keywords: Pycnodysostosis; Ossification of yellow ligament; Cathepsin K

Introduction

Pycnodysostosis is an autosomal recessive disorder characterized by osteosclerosis, small stature, acro-osteolysis of the distal phalanges, loss of the mandibular angle, separated cranial sutures with open fontanels, and frequent fractures [1,2]. One identified cause of the disease is reduced activity of the cysteine protease cathepsin K [2,3]. Here, we report a case of pycnodysostosis with ossification of the yellow ligament (OYL) in the lower thoracic and upper lumbar spine. We also identified a mutation in the cathepsin K gene. The patient provided informed consent for publication of data concerning this case.

Case Report

A 48-year-old woman presented to our hospital with severe gait disturbance. She had a two year history of left leg numbness, and her gait had gradually deteriorated over the 6 months prior to presentation. On neurologic exam, deep tendon reflexes in both legs were markedly increased. Manual muscle testing revealed generalized weakness (Grade 4 of 5) throughout the lower extremities. Sensation was impaired below the T8 level. She also was experiencing urinary incontinence and was hardly able to walk due to severe spasticity of the lower extremities. Based on the neurological findings, we concluded that she had a myelopathy below the T8 level.

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Plain radiographs of the spine showed multilevel OYL in the lower thoracic and upper lumbar spine and spondylolysis in L4 and L5 vertebrae (Fig. 1). Magnetic resonance imaging (MRI) showed mild spinal canal stenosis at T7/8, T10/11, and T11/12, and severe stenosis at T8/9, T9/10, and L1/2 (Fig. 2). Computed tomography

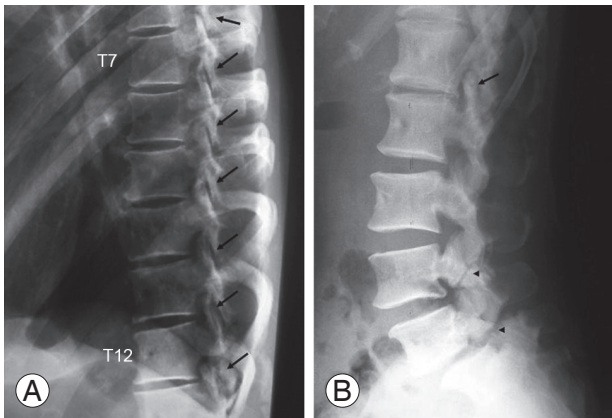


Fig. 1. Lateral radiographs of the thoracic (A) and lumbar (B) spine show ossification of the yellow ligament at T6/7, T7/8, T8/9, T9/10, T10/11, T11/12, and L1/2 (arrows), and spondylolysis at L4 and L5 (arrow heads).

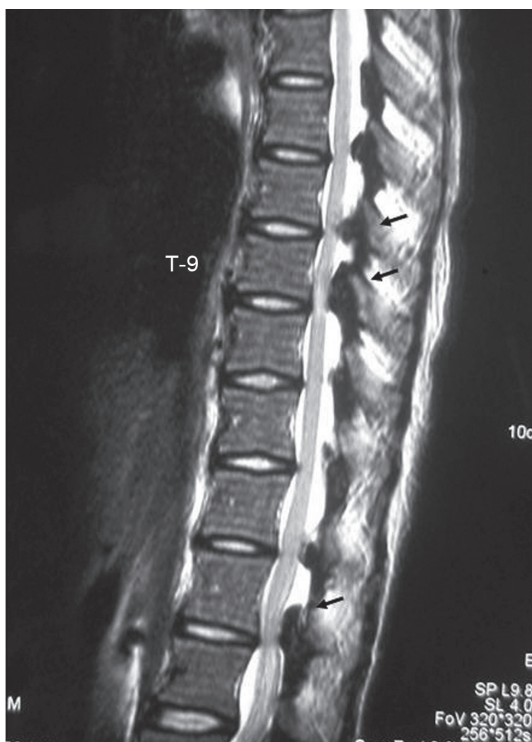


Fig. 2. Sagittal T2-weighted magnetic resonance imaging shows multilevel spinal canal stenosis at T6/7, T7/8, T8/9, T9/10, T10/11, T11/12, and L1/2. The stenosis at T8/9, T9/10, and L1/2 is severe (arrows).

clearly showed OYL at these levels (Fig. 3). We concluded that her gait disturbance and urinary incontinence were caused by thoracic and lumbar spinal canal stenosis due to OYL.

Although she had several common features of pycnodysostosis, such as frequent lower leg fractures, separated cranial sutures with open fontanel, and high bone density on radiographs, pycnodysostosis had not been diagnosed previously. Since cathepsin K gene mutations have been reported as a cause of pycnodysostosis [3-7], a DNA sequence analysis of the gene was performed. As shown in Fig. 4A, revealing a deletion of the genomic DNA nucleotide 426 T in exon 5. This mutation caused a frame shift at amino acid 142 (Fig. 4B), resulting in a stop codon at amino acid 160. This mutation is identical to that described in a report by Yamagiwa et al. [8] Based on this result, we diagnosed pycnodysostosis with a cathepsin K gene mutation.

Surgery was performed while evoked spinal cord potentials were monitored. Because the MRI revealed severe spinal cord compression due to OYL at T8/9, T12/L1, and L1/2 we chose to perform a total laminectomy at T8, T9,

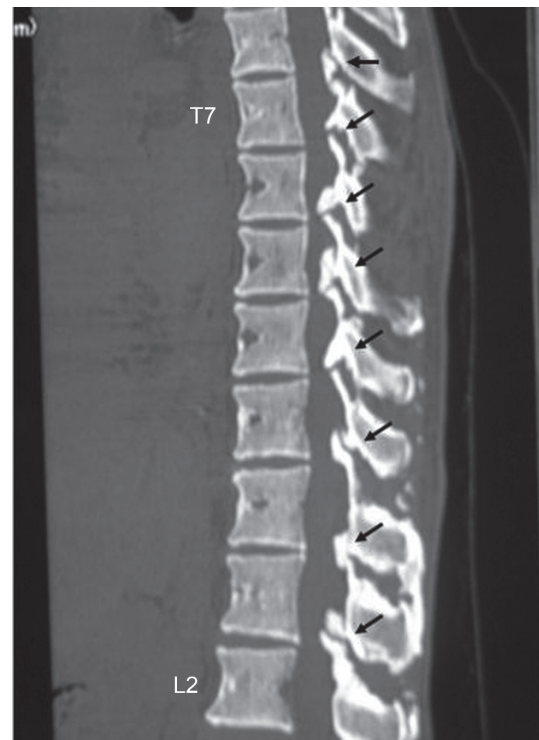


Fig. 3. Computed tomography clearly shows ossification of the yellow ligament at T6/7, T7/8, T8/9, T9/10, T10/11, T11/12, T12/L1, and L1/2 (arrows).

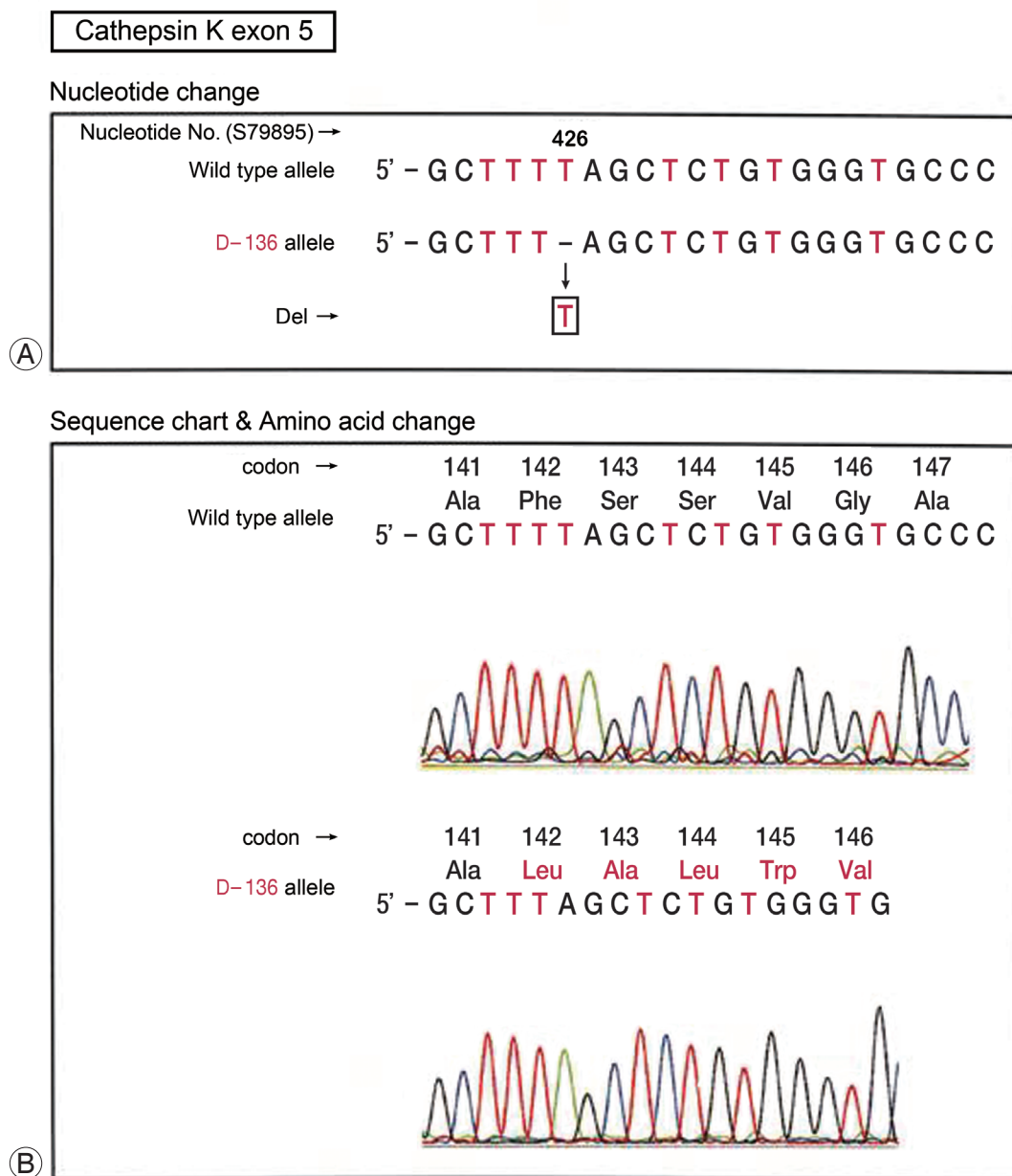


Fig. 4. (A) The results of DNA sequence analysis show a deletion of the genomic DNA nucleotide 426T. (B) This mutation causes a stop codon at amino acid 160.

and L1 and a partial laminectomy at T10/11 and T11/12.

Postoperatively, she was able to walk with a walker at three weeks, and with a Lofstrand crutch after three years.

Discussion

Spinal disorders in pycnodysostosis have been described in several reports. These include spondylolysis and other deformities, as reported by Beguiristain et al. [1,9,10]. To our knowledge, there have been no reports of pycnodys-

ostosis with OYL. Ossification of the spinal ligaments, such as ossification of the posterior longitudinal ligament (OPLL) and OYL are common in Japan and throughout Asia [11,12]. These sometimes compress the spinal cord and cauda equina, leading to various neurological disorders, from myelopathy to cauda equina syndrome. The mechanisms causing ligament ossification have been extensively researched [12]. The involvement of many growth factors and cytokines, including bone morphogenic proteins and transforming growth factor- β , have

been demonstrated in various histochemical and cytochemical analyses of ossified ligaments. Gene analysis studies have identified specific polymorphisms in several collagen genes, including type VI and XI collagens, that may be associated with OPLL [11,12]. In addition, several transcription factors regulating cellular differentiation may play an important role [11,12]. The exact mechanism, however, remains unclear.

In our patient, multilevel OYL was formed in pycnodysostosis leading to a severe gait disturbance. *In vitro* experiments have shown that ligament cells from patients with OPLL have some osteoblastic function [12]. In addition, mineral apposition and bone formation rates are increased in cathepsin K-deficient mice [7,13]. Based on these reports, we hypothesize that multilevel OYL can develop in pycnodysostosis by the following mechanism: a cathepsin K deficiency could lead to increased production of bone growth factors, which promote ossification of the spinal ligament by ligament cells with osteoblastic features.

This report demonstrates the OYL can develop in patients with pycnodysostosis and that treatment by laminectomy may relieve associated neurological problems. To supplement this initial case report, further studies are required to determine whether patients with pycnodysostosis have an increased risk of developing spinal ligament ossification.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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