Calcium pyrophosphate dihydrate of the ligamentum flavum in the cervical spine – A review of the literature

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ABSTRACT

Background: Calcium pyrophosphate dihydrate (CPPD) deposition, also known as pseudogout, in the cervical ligamentum flavum (CLF), is a rare disease which can cause spinal cord signaling changes leading to rapid deterioration in function. The natural history of cervical myelopathy as a result of CPPD deposition within the CLF is not well understood. Our objective is to describe the presentation, imaging findings, and treatment options of CPPD deposition or pseudogout of the cervical spine.

Methods: Using PubMed, we analyzed studies published from 1978 to 2022. Key words used were “pseudogout,” “CPPD deposit disease,” “cervical yellow ligament,” “CLF,” and “cervical spine.” We excluded “crowned dense syndrome” and “ossification of ligament flavum.” Using a department database, we queried for patients treated for CPPD of the cervical spine.

Results: Twenty clinical studies on CPPD of the cervical spine with 69 patients aged between 15 and 92 years (mean = 72) were identified. Neck pain and numbness of the hands were the most common symptoms. Diabetes mellitus and hypertension were the most common comorbidities. Males and females were affected at equal rates. C4-C5 and C5-C6 were the most affected segments. Earlier surgical treatment produced better outcomes. A laminectomy and fusion or laminoplasty were the most common procedures performed with most patients experiencing some return of neurologic function.

Conclusion: Although rare, CPPD deposit disease in the CLF should be readily considered as a differential diagnosis due to the continuously aging population. CPPD's progressively worsening nature makes an early diagnosis and treatment important in improving the patient's overall quality of life.

Keywords: Calcium pyrophosphate dihydrate, Cervical fusion, Cervical laminectomy, Cervical stenosis, Laminoplasty, Ligamentum flavum, Myelopathy

INTRODUCTION

Calcium pyrophosphate dihydrate (CPPD) deposit disease, also known as pseudogout and formerly known as articular chondrocalcinosis, was first defined by Zitnan and Sit'aj in 1958. In 1962, Kohn et al. differentiated pseudogout from gout through the use of compensated polarized microscopy which showed CPPD had a weakly positive birefringence and rhomboidal shape. Similar to gout, pseudogout can present in a multitude of locations including articular cartilage surfaces, joint capsules, ligaments, and intervertebral discs. However, since the first described case of CPPD deposition in the ligamentum flavum causing dorsal spinal cord compression, only few accounts of
CPPD deposition into the cervical ligamentum flavum (CLF) have been reported.[3]

The natural history of cervical myelopathy as a result of CPPD deposition within the CLF is not well understood.[20] As such, the consideration of CPPD deposit disease in CLF as a differential diagnosis is difficult[14,30] leading to likely many undiagnosed cases.[20] A lack of appropriate diagnosis can affect treatment choice and prognosis. To the best of our knowledge, no literature review to date on CPPD of the cervical spine has been performed. Our objective was to describe the presentation, imaging findings, and treatment options of CPPD deposition or pseudogout of the cervical spine. We also present case reports of two female patients aged 60–70 years old undergoing surgery for CPPD of the cervical spine.

SYNOPSIS OF INCLUDED STUDIES

A total of 20 clinical studies on CPPD deposit disease in the CLF were identified with 69 patients included for analysis. We analyzed all clinical studies published before 2022. The first report was in 1978 and the most recent in 2021. We identified articles using PubMed with references listed as peer-reviewed publications. Key words used included “pseudogout,” “CPPD deposit disease,” “cervical yellow ligament,” “CLF,” and “cervical spine.” We excluded “crowned dense syndrome” and “ossification of ligament flavum.” Table 1 shows a summary of the literature and outcomes in patients with CPPD deposit disease of the CLF.

CASE DESCRIPTIONS

Using the department’s database, two cases of CPPD deposit disease in the CLF were identified. The clinical and histological evidence is discussed.

Case 1

A 60-year-old woman, with cervical myelopathy, presenting with balance and gait abnormalities. Magnetic resonance imaging (MRI) and computed tomography (CT) identified a dorsal compression of the spinal cord emanating from the ligamentum flavum at the C4-C5, C5-C6, and C6-C7 levels [Figure 1]. The patient has a medical history of Type 2 diabetes mellitus and renal transplant. She underwent a C4-C6 laminoplasty with instrumentation and C3 and C7 partial laminectomies [Figure 2]. Tissue sample of the compressive lesion was collected and sent to pathology. Under polarized light microscopy, rhomboidal-shaped crystal deposits were identified with weakly positive birefringence confirming the diagnosis of CPPD [Figure 3]. Patient’s symptoms resolved postoperatively. She is doing well at 2-year follow-up.

Case 2

A 70-year-old woman, with cervical myelopathy, presenting with balance and gait abnormalities resulting in falls. MRI and CT demonstrated a dorsal based compression of the spinal cord emanating from the ligamentum flavum at the C4-C5 [Figure 4]. She has a medical history of Type 1 diabetes mellitus, coronary artery disease, and hypothyroidism. The patient underwent a C3-C6 laminectomy and instrumented posterior spinal fusion [Figure 5]. The specimen was sent to pathology and under polarized light microscopy demonstrated rhomboidal crystal deposits with weakly positive birefringence confirming the diagnosis of CPPD. The patient’s symptoms were resolved postoperatively and are doing well at 4-month follow-up.

EPIDEMIOLOGY AND RISK FACTORS

Various factors play a role in the development of CPPD in the CLF such as aging, metabolic diseases, mechanical stress, and endocrine imbalance.[20] The presentation of CPPD in the CLF is a rare occurrence; however, it has been disproportionately diagnosed in the Asian population.[6,13,14,19,24]

Overall, aging is a major risk factor for CPPD deposit disease in the CLF. The prevalence of CPPD deposit disease increases from 3.7% to 17.5% as age groups increase from 55–59 to 80–84, respectively.[28] We suspect the prevalence of CPPD in the CLF to be higher as most surgeons do not routinely have the intraoperative tissue samples sent to pathology to confirm diagnosis. CPPD deposit disease is said to have an incidence rate of 1/1000 with half of the diagnosis affecting those over 80 years of age.[31] The general deposit of CPPD crystals in any part of the body was shown to have a mean age of 63.7 years.[28] The mean age of those with CPPD deposit disease in the CLF is reported to be higher at a mean age 73.2 years,[20] which is similar to our findings of 72 years. As CPPD tends to deposit into multiple joints[22] and shows to have a later onset of deposition into the CLF,[20] it is important to monitor patients from the onset of diagnosis to ensure appropriate treatment.

While CPPD in the CLF has a mean onset age of 72–73 years, on rare occasions, it can be observed in the pediatric population. Morino et al. 2016[21] reported a case of CPPD deposit disease in the CLF of a 15-year-old male with Coffin-Lowry syndrome, an X-linked semi-dominant condition characterized by intellectual delay and physical deformities. In Coffin-Lowry syndrome, collagen synthesis is affected reducing CLF’s elasticity and increasing CPPD deposit disease.[33] The progression of symptoms followed a similar course as seen in the elderly population.[14] However, this is the only known report of the disease’s appearance in this population.

Another risk factor that is commonly reported is gender.[7,20,24,26,28,34] There has been conflicting evidence of increased prevalence of CPPD in the CLF in men and women.[6,10,13]
| Authors                        | Age/sex | Comorbidities                                    | Symptoms                                                                 | Duration of symptoms before admission | Affected level | Type of surgery | Level of surgery | Outcomes                           |
|-------------------------------|---------|--------------------------------------------------|--------------------------------------------------------------------------|---------------------------------------|----------------|-----------------|------------------|------------------------------------|
| Ellman et al. (1978)          | 70 y/M  | --                                               | --                                                                       | --                                    | --             | --              | --               | --                                |
| Kawano et al. (1980)          | 63 y/F  | --                                               | Gait disturbance                                                         | 4 months                             | C3-C4, C4-C5, C5-C7 | Decompression and laminectomy      | C2-T1             | Discharged 4-month postoperative |
| Nagashima et al. (1981)       | 1) 74 y/F | 1) Diabetes Mellitus, hypertension, chronic hepatitis, cervical and thoracic candidiasis, bronchospnemonia | 1) Claudications of both hands, numbness in distal legs and arms, and pain radiation down arm on neck flexion, Fifteen months – bilateral finger numbness, 9 months – plantar numbness, and 2 months – inability to write | 1) 15 months | 1) C4-C6, C5-C6 | 1) Decompression and laminectomy | C1-C4             | Recovery by morning of surgery 1-month postoperative – 80% recovered numbness of arm and leg Two years and 2 months – complete recovery of neurological symptoms |
|                               | 2) 61 y/M | 2) Diabetes Mellitus, hypertension, chronic hepatitis | 2) Claudications of both hands, numbness in distal legs and arms, and pain radiation down arm on neck flexion, Fifteen months – bilateral finger numbness, 9 months – plantar numbness, and 2 months – inability to write | 2) 21 month | 2) C3-C4, C4-C5 | 2) Decompression and laminectomy | C2-C5             | --                                |
|                               | 3) 65 y/F | 3) Diabetes Mellitus, hypertension, chronic hepatitis | 3) Claudications of both hands, numbness in distal legs and arms, and pain radiation down arm on neck flexion, Fifteen months – bilateral finger numbness, 9 months – plantar numbness, and 2 months – inability to write | 3) 3 months | 3) C5-C6 | 3) Laminectomy | C3-C6             | --                                |
| Ogata et al. (1980)           | 1) 61 y/M | 1) Diabetes Mellitus                             | 1) Claudications of both hands, numbness in distal legs and arms, and pain radiation down arm on neck flexion, Fifteen months – bilateral finger numbness, 9 months – plantar numbness, and 2 months – inability to write | 1) 6 months | C2-C4 | Decompression, laminectomy | C1-C5             | --                                |
|                               | 2) 65 y/F | 2) Diabetes Mellitus                             | 2) Claudications of both hands, numbness in distal legs and arms, and pain radiation down arm on neck flexion, Fifteen months – bilateral finger numbness, 9 months – plantar numbness, and 2 months – inability to write | 2) 6 months | C2-C4 | Decompression, laminectomy | C1-C5             | --                                |
|                               | 77 y/F   | --                                               | --                                                                       | --                                    | --             | --              | --               | --                                |
| Kawano et al. (1987)          | 64 y/F   | --                                               | Gait disturbance                                                         | 6 months                             | C3-C4, C5-C6   | Decompression, laminectomy         | C3-C6             | Neurological symptoms improved 3-month postoperative |
| Kawai et al. (1996)           | 74 y/F   | --                                               | --                                                                       | --                                    | --             | --              | --               | --                                |
| Gomti and Chau. (1998)        | 67 y/F   | --                                               | Gait disturbance                                                         | 6 months                             | C3-C5 | Decompression, laminectomy         | C3-C5             | --                                |
| Ciret et al. (1999)           | 76 y/F   | --                                               | Gait disturbance                                                         | 3 weeks                              | C4-C5 | Laminectomy                     | C5                | Discharged 9 days post surgery    |
| Sengoku et al. (2000)         | 52 y/M   | --                                               | --                                                                       | C7-T1                                | Decompression, laminectomy | C4-C6 | Rapid dissipation of sensory disturbance and weakness in the upper and lower extremities Discharged 10 days post surgery with remarkable signs |
| Chen et al. (2013)            | 73 y/F   | --                                               | Gait disturbances, neck stiffness, and muscle weakness, claudications in both hands | 2 months                             | C5-C6 | Decompression, laminectomy         | C5-C6             | Discharged 10 days post surgery with remarkable signs |
| Malakosan and Karuppatanwar (2000) | 1) 70 y/F | 1) --                                           | 1) Claudications of both hands, numbness in distal legs and arms, and pain radiation down arm on neck flexion, Fifteen months – bilateral finger numbness, 9 months – plantar numbness, and 2 months – inability to write | 1) --                                | --             | --              | --               | --                                |
|                               | 2) 55 y/F | 2) Diabetes Mellitus                             | 2) Claudications of both hands, numbness in distal legs and arms, and pain radiation down arm on neck flexion, Fifteen months – bilateral finger numbness, 9 months – plantar numbness, and 2 months – inability to write | 2) --                                | --             | --              | --               | --                                |
| Jain et al. (2006)            | 74 y/F   | --                                               | Gait disturbance                                                         | 6 months                             | C3-C6 | Decompression, laminectomy         | C3-C6             | Neurological symptoms improved after surgery Pain and paresthesia followed later Improved muscle strength |

Table 1: Cases in the literature review from 1978 to 2021 reported to have CPPD deposit disorder in the CLF.
| Authors          | Age/sex | Comorbidities         | Symptoms                                                                 | Duration of symptoms before admission | Affected level | Type of surgery | Level of surgery | Outcomes       |
|-----------------|---------|-----------------------|--------------------------------------------------------------------------|----------------------------------------|----------------|----------------|------------------|----------------|
| Mwaka et al. (2009) | 1) 41 y/F | --                   | 1) U/L numbness, gait abnormality, motor and sensory deficient, and abnormal reflexes | --                                     | 1) C4-C6       | 1) Laminoplasty | 1) excellent – 0.3 years |              |
|                 | 2) 79 y/M | 2)                   | 1) U/L numbness, gait abnormality, motor and sensory deficient, and abnormal reflexes | --                                     | 2) C3-C7       | 2) Laminoplasty | 2) fair – 1.3 years |              |
|                 | 3) 67 y/F | 3)                   | 2) L pain, U/L numbness, motor weakness and sensory deficient, gait instability, abnormal reflex, and Madder dysfunction | 3) C3-C7                               | 3) C3-C7       | 3) Laminoplasty | 3) poor – 5.3 years |              |
|                 | 4) 65 y/M | 4)                   | 3) U pain, numbness and sensory deficit, gait instability, and arm instability | 4) C2-C4                               | 4) C2-C4       | 4) Laminoplasty | 4) excellent – 2.1 years |              |
|                 | 5) 75 y/F | 5) Diabetes Mellitus  | 5) Diabetes Mellitus, U/L numbness, U/L numbness, motor and sensory deficit, gait instability, abnormal reflex, and Madder dysfunction | 5) C3-C4                               | 5) C3-C4       | 5) Laminoplasty | 5) excellent – 9.3 years |              |
|                 | 6) 75 y/F | 6)                   | --                                                                       | 6) C6-C8                               | 6) C6-C8       | 6) Laminoplasty | 6) good – 2.5 years |              |
|                 | 7) 75 y/F | 7) Diabetes Mellitus  | 7) Diabetes Mellitus, U/L numbness, motor and sensory deficit, gait instability, abnormal reflex, and arm radicular sign | 7) C5-C7                               | 7) C5-C7       | 7) Laminoplasty | 7) good – 0.3 years |              |
|                 | 8) 50 y/M | 8)                   | --                                                                       | 8) C4-C6                               | 8) Laminoplasty | 8) C4-C6       | 8) excellent – 0.5 years |              |
|                 | 9) 76 y/M | 8)                   | --                                                                       | 9) C3-C5                               | 9) Laminoplasty | 9) C3-C5       | 9) good – 0.9 years |              |
|                 | 10) 79 y/M | 9)                   | --                                                                       | 10) C3-T1                              | 10) Laminoplasty | 10) C3-T1     | 10) good – 3.0 years |              |
|                 | 11) 84 y/M | 10)                  | --                                                                       | 11) C3-C7                              | 11) Laminoplasty | 11) C3-C7     | 11) fair – 0.3 years |              |
|                 | 12) 83 y/F | 11)                  | --                                                                       | 12) C3-C4                              | 12) Laminoplasty | 12) C3-C4     | 12) good – 0.3 years |              |
|                 | 13) 75 y/F | 12)                  | 12) Diabetes Mellitus                                                    | 12) C3-C4                              | 13) Laminoplasty, C5 subtotal | 13) C4-C6     | 13) fair – 1.5 years |              |
|                 | 14) 68 y/F | 13)                  | 13) Diabetes Mellitus                                                    | 13) C4-C6                              | 14) Laminoplasty | 14) C4-C5     | 14) good – 7 years |              |
|                 | 15) 76 y/F | 14)                  | 14) Diabetes Mellitus                                                    | 14) C4-C5                              | 15) Laminoplasty | 15) C4-C6     | 15) good – 0.2 years |              |
|                 | 16) 74 y/F | 15)                  | 15) Diabetes Mellitus                                                    | 15) C4-C6                              | 16) Laminoplasty | 16) C4-C6     | 16) excellent – 0.3 years |              |
|                 | 17) 59 y/F | 16)                  | 16) Diabetes Mellitus                                                    | 16) C4-C6                              | 17) Laminoplasty, C5-6 ADIF | 17) C5-C7     | 17) good – 0.2 years |              |
|                 | 18) 71 y/M | 17)                  | 17) Diabetes Mellitus                                                    | 17) C5-C7                              | 18) Laminoplasty | 18) C4-T1     | 18) good – 3.0 years |              |
|                 | 19) 79 y/M | 18)                  | 18) Diabetes Mellitus                                                    | 18) C4-T1                              | 19) Laminoplasty | 19) C5-C7     | 19) fair – 1.6 years |              |
|                 | 20) 86 y/M | 19)                  | 19) Diabetes Mellitus                                                    | 19) C5-C7                              | 20) Laminoplasty | 20) C5-C5     | 20) fair – 1.6 years |              |
|                 | 21) 70 y/F | 20)                  | 20) Diabetes Mellitus                                                    | 20) C5-C5                              | 21) Laminoplasty | 21) C5-C6     | 21) good – 0.8 years |              |
|                 | 22) 58 y/M | 21)                  | 21) Diabetes Mellitus                                                    | 21) C5-C6                              | 22) Laminoplasty, C4-5 ADIF | 22) C4-C5     | 22) good – 0.3 years |              |
|                 | 23) 59 y/F | 22)                  | 22) Diabetes Mellitus                                                    | 22) C4-C5                              | 23) Laminoplasty | 23) C5-C6     | 23) excellent – 0.5 years |              |
|                 | 24) 78 y/M | 23)                  | 23) Diabetes Mellitus                                                    | 23) C5-C6                              | 24) Laminoplasty | 24) C4-C7     | 24) good – 0.2 years |              |
|                 | 25) 77 y/F | 24)                  | 24) Diabetes Mellitus                                                    | 24) C4-C7                              | 25) Laminoplasty | 25) C4-C6     | 25) excellent – 0.2 years |              |
|                 | 26) 76 y/F | 25)                  | 25) Diabetes Mellitus                                                    | 25) C4-C6                              | 26) Laminoplasty | 26) C3-C4     | 26) good – 0.2 years |              |

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| Table 1: (Continued) |
|----------------------|
| **Authors** | **Age/sex** | **Comorbidities** | **Symptoms** | **Duration of symptoms before admission** | **Affected level** | **Type of surgery** | **Level of surgery** | **Outcomes** |
| Shojiama et al. (2010)[29] | 1) 83 y/F | -- | 1) Acute posterior neck pain and stiffness | 2) 78 y/M | -- | 1) Laminectomy | 1) No | Surgery |
| | 2) 78 y/M | -- | 1) Acute posterior neck pain and stiffness | 2) 78 y/M | -- | 2) Laminectomy | 2) No | Symptoms relieved within 1–3 weeks |
| | 3) 92 y/F | -- | 1) Acute posterior neck pain and stiffness | 3) 75 y/F | -- | 3) Laminectomy | 3) No | Symptoms relieved within 1–3 weeks |
| | 4) 65 y/F | -- | 1) Acute posterior neck pain and stiffness | 4) 78 y/M | -- | 4) Laminectomy | 4) No | Symptoms relieved within 1–3 weeks |
| Kolayshi et al. (2010)[30] | 70 y/F | -- | Neck stiffness – inability to move | Neck pain | First admission 1–4 days | C5-C6 | Laminectomy | C5-C6 | Stabilization within 3 weeks, reduced neck pain. |
| | -- | -- | -- | -- | Second admission | C2-T3 | -- | -- | No neck pain post 7 months. |
| | -- | -- | -- | -- | -- | -- | -- | -- | Complete relief of neck pain post 7 years. |
| Morino et al. (2016)[31] | 15 y/M | Coffin-Lowry syndrome | Cervical myelopathy | Queritrifogin | 2 weeks | Decompression, laminectomy | C1-C7 | Recovery of upper and lower extremity |
| | -- | -- | Spastic tetraplegia | -- | -- | -- | -- | -- | 8-year follow-up |
| Kimura et al. (2020)[32] | 78 y/M | Spinal cord injury - C6 | Acute neck pain | Cervical Myelopathy | Tetraplegia | -- | C3-C5 | Laminectomy and laminoplasty | C4-C5 | Postoperative uneventful |
| | -- | -- | -- | -- | -- | -- | -- | -- | Improvement on 1 year follow up |
| Luo et al. (2021)[33] | 65 y/F | Hypertension | Neck pain | Bilateral finger numbness | 6 months | C4-C5 | Laminectomy | -- | -- |
| | -- | -- | -- | left-sided upper extremity weakness | -- | -- | -- | -- | -- |
| Lu et al. (2021)[34] | 1) 70 y/M | 1) Diabetes Mellitus | 1) Neck pain and myelopathy | -- | 1) Decompression with fusion | C3-C7 | -- | 1) 1–2 |
| | 2) 85 y/M | 2) Absent | 2) Myeloscleroticus | 1) 6 months | 2) Decompression | C1-C7 | -- | 2) 1 |
| | 3) 59 y/M | 3) Hypertension, Arthritisma | 3) Myeloscleroticus | 2) 6 months | 3) Decompression | C3-C6 | -- | 3) 2–3 |
| | 4) 69 y/M | 4) Diabetes Mellitus, Hypertension | 4) Myelopathy | 3) 6 months | 4) Decompression with fusion | C1-C3, C7-T1 | -- | 4) 2–3 |
| | 5) 66 y/M | 5) Hypertension, Hyperlipidemica | 5) Neck and myeloscleroticus | 4) 10 months | 5) Decompression with fusion | C5-C6 | -- | 5) 2–3 |
| | 6) 72 y/M | 6) Diabetes Mellitus, Hypertension | 6) Neck pain and radiculopathy | 5) 10 months | 6) Decompression | C6-C7 | -- | 6) 1–2 |
| | 7) 86 y/M | 7) Hypertension, CVD | 7) Neck pain and radiculopathy | 6) 6 months | 7) Decompression | C6-C7 | -- | 7) 1 |
| | 8) 79 y/M | 8) -- | 8) Myelopathy | 7) 6 months | 8) Decompression | C2-C5 | -- | 8) 2–3 |
| | 9) 87 y/M | 9) Hypertension, CVPD | 9) Neck pain and myeloscleroticus | 8) 2 months | 9) Decompression | C6-C7 | -- | 9) 2–3 |
| | 10) 73 y/M | 10) Diabetes Mellitus, Hypertension | 10) Myelopathy | 9) 10 months | 10) Decompression | C5-C6 | -- | 10) 1–2 |
| | 11) 78 y/F | 11) Hypertension, Cardiovascular | 11) Neck pain and myeloscleroticus | 10) 6 months | 11) Decompression | C3-C6 | -- | 11) 1 |
| | 12) 70 y/F | 12) Myelopathy | 12) Neck pain and myeloscleroticus | 11) 2 months | 12) Decompression | C4-C7 | -- | 12) 1 |
| | 13) 77 y/M | 13) Diabetes Mellitus. | 13) Neck and myeloscleroticus | 12) 2 months | 13) Decompression | C4-C7 | -- | 13) 1 |
| | 14) 81 y/M | 14) Cardiovascular Disease | 14) Neck pain and myelopathy | 13) 6 months | 14) Decompression | C4-C7 | -- | 14) 1 |
| | 15) 67 y/F | 15) Hypertension, End stage renal disease | 15) Myeloscleroticus | 14) 2 months | 15) Decompression with fusion | C5-C7 | -- | 15) 1 |
| | 16) 81 y/F | 16) Myeloscleroticus | 16) Neck pain and myeloscleroticus | 15) 15 months | 16) Decompression | C4-C7 | -- | 16) 2–3 |
| | 17) 78 y/F | 17) Hypertension | 17) Neck pain and radiculopathy | 16) 7 months | 17) Decompression with fusion | C1-C3, C6-C7 | -- | 17) 1 |
| | 18) 77 y/F | 18) Hypertension, End stage renal disease | 18) Neck pain and m-discalypathia | 17) 6 months | 18) Decompression | C5-C6 | -- | 18) 1–2 |
| | 19) 77 y/F | 19) Diabetes Mellitus | 19) Diabetes Mellitus | 18) 12 months | 19) Decompression | C5-C6 | -- | 19) 1–2 |
| | 20) 77 y/F | 20) Hypertension | 20) Hypertension | 19) 18 months | 20) Decompression | C5-C6 | -- | 20) 1–2 |

U/L: Upper extremity, Lower extremity, CPPD: Calcium pyrophosphate deposition, CLF: Cervical ligamentum flavum
However, we found similar results as Richette et al. in 2009 with similar prevalence between men and women [Table 2].

Although the direct cause of pseudogout is still unclear, some reported that metabolic risk factors for CPPD deposit disease in the CLF are hyperthyroidism, hypothyroidism, hyperparathyroidism, osteoarthritis, diabetes mellitus, artherosclerosis, hypertension and hemochromatosis. Wilson’s disease, hypophosphatasia, hypomagnesemia, and loop diuretics use. Hyperparathyroidism, hemochromatosis, hypothyroidism, and hypomagnesium have the strongest association with CPPD deposition in the CLF. In addition, CPPD deposition can also be associated with trauma and surgery. In our review [Table 3], we found the comorbidities most associated with CPPD deposition in the CLF were diabetes mellitus and hypertension. However, it is important to understand that CPPD in the CLF appears most commonly in the elderly population who often have multiple comorbidities at baseline and as such it is difficult to determine a direct relationship.
The cervical spine is an area of high mobility. As such, the ligamentum flavum is highly elastic in this section of the spine leaving it susceptible to microscopic tears. The thickness of the ligamentum flavum increases with age and accumulation of mechanical stress which is associated with increased fibrosis and decreased elastic fibers. Transforming growth factors-beta (TGF-B) may stimulate fibrosis particularly during early hypertrophy. As the ligamentum flavum is in direct contact with the dura of the spinal cord, abnormal hypertrophy within this ligament has the potential for direct compression on the dorsal aspect of the spinal cord.

The origin of CPPD deposit disease in the CLF is unknown but three factors may influence its deposition: (i) metabolic disorders; (ii) sporadic inheritance; and (iii) familial inheritance. Sporadic acquisition is most common while genes localized on chromosome 5p are shown to be responsible for familiar inheritance. Sporadic acquisition is hypothesized to occur through two methods: (1) overproduction or decreased removal of CPPD crystals from underlying collagen and (2) secondary to trauma or previous surgery causing intracellular pyrophosphate release from intracellular space into the extracellular matrix. Kimura et al. detailed a trauma case of 78-year-old male who fell and injured his cervical spine. Following his fall, 4 days later, he became feverish, began having neck pain, and experiencing tetraplegia. Through tissue biopsy, CPPD deposit in the CLF diagnosis was made and an appropriate treatment course was followed.

Morphologically, the central region of the CLF is the primary area affected as it becomes surrounded by denigrative fibers due to CPPD deposition. Wide amorphous fibrotic areas with a reduced number of elastic fibers and increased collagenous tissue were frequently observed in pathologic CLF. Chondrocytes were found around the deposits of calcium scattered among the matrix of the ruptured elastic fiber bundles. Furthermore, small blood vessel was shown to proliferate within the periphery of the calcified lesion. Cytokines such as basic fibroblast growth factors and TGF-B were found in the hypertrophic chondrocytes and mesenchymal cells that infiltrated the
area which surround the calcified deposit. Phagocytosis of polymorphonuclear leukocytes and release of inflammatory factors then lead to acute inflammation at the ligamentum flavum. CPPD is frequently associated with generalized collagen degeneration. With the CLF’s thickness, a small nodular lesion within the collagenous ligament thickening can lead to compression of the dorsal column of the spinal cord producing myelopathic symptoms. The C5 segment shows the highest dynamic stress in the cervical region with the elastic tissue most prone to degeneration. Based on our review, the C5 segment (54%) is the most affected segment and most likely location in which CPPD crystals deposited into the CLF. Furthermore, C4-C5 and C5-C6 were reported as the most frequently diseased segments. Repetitive stretch, trauma, and advanced age are contributing factors to crystal deposition in the cervical spine.

**DIAGNOSIS**

The primary methods of diagnosis of CPPD in the CLF are through a combination of symptomatology, MRI, CT, and histopathology.

| Table 2: Patient demographics. Summary of demographics |
|-----------------------------------------------|
| 20 clinical studies                        69 Patients |
| # of Men                                    33 (47.9%) |
| # of Women                                  36 (52.1%) |
| Mean Male age                                71.8 years (range=15–87) |
| Mean Female age                             72.2 years (range=55–92) |

| Table 3: Risk factors for CPPD deposit disease of the CLF. |
|-----------------|---|
| Predisposing conditions | n (%) |
| Diabetes mellitus | 18 (39) |
| Hypertension      | 15 (31) |
| COPD              | 2 (4)  |
| Cardiovascular disease | 2 (4)  |
| End stage renal disease | 2 (4) |
| Hyperthyroidism   | 1 (2)  |
| Arrhythmia        | 1 (2)  |
| Hyperuricemia     | 1 (2)  |
| Spinal cord injury| 1 (2)  |
| Coffin- Lowry syndrome | 1 (2) |
| Osteoarthritis    | 1 (2)  |
| Epileptic seizures| 1 (2)  |

CPPD: Calcium pyrophosphate dehydrate, CLF: Cervical ligamentum flavum

The symptoms of CPPD deposit disorder are progressive in nature with global worsening and loss of function with time. Symptoms can vary from neck pain to myelopathic symptoms such as numbness of upper extremity, gait abnormalities, and bladder dysfunction. CPPD in the CLF creates a pathological lesion which compresses the cervical spinal cord dorsally leading to a more pronounced decrease in sensation. We observed the most common symptoms of CPPD in the CLF to be neck pain, numbness and weakness of the upper extremity, and gait disturbances. It is important to note that 10–20% of patients do not present with any symptoms. Therefore, CPPD deposition in these patients is typically discovered as an incidental finding.

CPPD deposition disease in the CLF is commonly mistaken for ossification of ligamentum flavum (OLF) which is more often centrally identified in the lower thoracic spine and generally localized to a single level. Differentiation of these two disorders is critical in making an appropriate diagnosis and the implementation of appropriate treatment. CPPD primarily depots in the cervical spine while OLF has no common location. CPPD typically affects multiple levels while OLF most often affects a single segment.

| Table 4: Summary of affected ligamentum flavum in 69 cases. |
|-------------------|
| Cervical segment   | n (%) |
| C1-C2             | 1 (0.07) |
| C2-C3             | 9 (7)  |
| C3-C4             | 29 (21) |
| C4-C5             | 40 (29) |
| C5-C6             | 35 (25) |
| C6-C7             | 19 (14) |
| C7-T1             | 5 (4)  |

| Table 5: Summary of cervical myelopathic symptoms in 69 clinical cases. |
|------------------|
| Symptoms         | n (%) |
| Neck pain        | 36 (16) |
| Numbness of upper extremity | 32 (14) |
| Upper extremity weakness | 31 (14) |
| Gait disturbance | 30 (13) |
| Hyperreflexia    | 24 (11) |
| Numbness of lower extremity | 21 (9)  |
| Myeloradiculopathy | 18 (8) |
| Bladder dysfunction | 9 (4)  |
| Myelopathy       | 8 (3.6) |
| Neck stiffness   | 6 (2.7) |
| Leg pain         | 4 (1.8) |
| Tetraplegia      | 1 (0.04) |
| Quadriplegia     | 1 (0.04) |
| Monoplegia       | 1 (0.04) |
| Paraplegia       | 1 (0.04) |
CPPD deposition does not extend to the posterior facet joints while OLF always extends to the posterior facet joint. CPPD deposition is not continuous with the lamina and OLF shows continuity with the lamina.\cite{16,20} CPPD lesions have a nodular-type appearance instead of a beak-like or mound-like appearance which is seen in OLF.\cite{6,19} Macroscopically, CPPD lesions present as a white chalky, rough, and granular substance with a consistency of pumice primarily observed in the dorsal aspect of the ligament with gradual extensions toward the dura.\cite{13,16,24}

Although gout and CPPD deposit disease present similarly in their ability to deposit crystals into joints, cartilage, and ligaments causing an inflammatory response,\cite{17} patients with CPPD have normal uric acid laboratory values.\cite{13,21,25} Gout is therefore more associated with monosodium urate monohydrate crystals in patients with elevated serum urate concentration.\cite{34} Once the CPPD lesion is extracted out of the CLF, the use of polarized light microscopy indicating a weakly positive birefringence is necessary to confirm a CPPD deposit disease diagnosis [Figure 3].\cite{17}

**IMAGING**

Sagittal CT [Figures 1a and 4a] of the cervical spine is the most effective way to diagnose CPPD in the CLF.\cite{33} It reveals a high density mass located in the interlaminar region of the ligamentum flavum. Advanced and detailed CT neuroimaging shows both hypertrophic and calcified ligaments including any severe spinal cord compression from the posterolateral aspect.

Sagittal and axial MRI with T1- and T2-weighted imaging [Figure 1b and c] is another effective methods of diagnosing CPPD in the CLF.\cite{24} MRI detects the level of spinal cord compression and other soft-tissue changes.\cite{19} Three common MRI diagnostic features of CPPD deposition disorder in the CLF were identified as: (1) isointense lesion in the T1-weighted image, (2) a mixed density mass in T2-weighted image, and (3) a peripheral enhancement on the post contrast MRI images.\cite{12}

CPPD nodules show low signal intensity in T1- and T2-weighted image surrounded by areas of high and medium signal intensity considered an appearance of edematous change. Lu et al. 2021\cite{20} described this as acute on chronic phenomenon as there was acute or subacute inflammation caused by the crystal deposits. However, 5-month post symptom presentation, CPPD lesions appear to no longer demonstrate medium to high signal intensity within the edematous region which may indicate long-term morphological changes.\cite{20} This could indicate a need for differing treatment methods in the acute versus chronic phases of CPPD.

**MANAGEMENT OF CPPD**

As discussed, prognostic factors of CPPD deposition disease in the CLF include age, comorbidities, rate of deterioration, severity and duration of symptoms, and spinal cord signal changes.

Management of CPPD deposition disease in the CLF is dependent on the course of the disease. Although CPPD crystals can cause inflammation, many patients do not present with abnormally high inflammatory markers.\cite{16} However, in the presence of abnormally high inflammatory factors such as C-reactive proteins, patients respond well to conservative methods such as NSAIDs, corticosteroids, and low-dose colchicine.\cite{16,30} Some patients have experienced symptom relief within 1–3 weeks of implementing conservative methods.\cite{30} Even so, symptoms may recur and worsen rendering non-operative and conservative methods ineffective long-term.\cite{15} In addition, when inflammatory markers are negative, which typically occurs later in the course of the disease, operative intervention by open decompression with either cervical laminectomy with fusion or laminoplasty has been shown to offer the best results [Figures 2 and 5].\cite{13,25}

A laminectomy is a highly effective method of relieving cervical myelopathy caused by CPPD lesion as the symptomatic lesions are typically confined to specific spinal segments.\cite{20} Decompression at those levels often results in the return of neurological function.\cite{34} However, intraoperative complications such as dural tears can occur due to CPPD lesions adherence to the dura matter.\cite{10} Although surgical decompression can produce great results and improve preoperative neurologic deficits, it is important to note that it is not a cure and some residual symptoms may persist.\cite{14} Depending on the degree and length of time, the spinal cord was compressed there may be irreversible damage that will persist despite decompression.\cite{10} Furthermore, patients should be monitored overtime to identify CPPD deposition in other areas of the ligamentum flavum.\cite{50}

Early surgical treatment produces better long-term outcome and return of neurological function.\cite{4,10} Patients with symptoms lasting under a 5-month duration showed the greatest and earliest improvement in neurological function after a laminectomy.\cite{20,25} In contrast, patients with symptoms lasting over 24 months demonstrated an inability to recover to presymptomatic levels.\cite{20} Therefore, early surgical intervention and diagnosis are critical to stop irreversible damage.

**CONCLUSION**

Although a rare condition, the prevalence of CPPD in the CLF indicates that it should be considered as a differential
diagnosis particularly as the age of the population increases. CPPDs’ progressively worsening nature makes an early diagnosis and treatment important in improving the patient’s overall quality of life and functional outcome.

Declaration of patient consent

Patients’ consent not required as patients’ identities were not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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