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Surgical Neurology International

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SNI: Neuropathology

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Review Article

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

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Received : 29 July 2022
Accepted : 21 September 2022
Published : 14 October 2022

DOI
10.25259/SNI_684_2022

Quick Response Code:

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 spine, 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.[36] In 1962, Kohn *et al.*[17] 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.[19,28] 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 lesion compressing 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.[6,13,18,19,24]

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.[35] 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]

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
Ellman *et al.* (1978)[7]	70 y/M	--	--	--	--	Decompression and laminectomy	--	--
Kawano *et al.* (1980)[13]	63 y/F	--	Gait disturbance Tingling sensation in the fingertips of both hands Muscle weakness of both hands Hyperreflexia of all extremities	4 months	C3-C4, C4-cC5, C6-C7	Decompression and laminectomy	C2-T1	Discharged 4-month postoperative Improved neurological signs
Nagashima *et al.* (1981)[25]	1) 74 y/F 2) 61 y/M 3) 65 y/F	1) Diabetes Mellitus, prehypertension 2)-- 3) Diabetes Mellitus, hypertension, chronic hepatitis, urinary tract infections, vaginal and cutaneous candidiasis, bronchopneumonia	1) Clumsiness 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) One year before admission pain radiation from neck to all four extremities. Eight month before s; neck pains while getting up in the morning. Two months before; cold dysesthesia. Gait disturbance. 3) Leg pain and paraplegia, monoplegia of the right arm. Loss of sensory below C5	1) 15 months 2) 1 year 3) 5 months	1) C4-C5, C5-C6 2) C-3-C4, C4-C5 3) C3-6	1) Decompression and laminectomy 2) Laminectomy 3) Laminectomy	1) C4-C7 2) C3-C5 3) C2-T1	1) 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) Twenty-two-month postoperative – no postoperative symptoms 3) Pain relief postoperative morning.
Ogata *et al.* (1984)[26]	1) 61 y/M 2) 65 y/F	--	--	--	1) C3-C5 2) C3-C4	Decompression, laminectomy	1) C3-C5 2) C3-C4	--
Berghausen *et al.*(1987)[2]	77 y/F	--	Numbness in hand and feet Neck pain progressive unsteadiness, weakness and loss of proprioception	6 months	C2-C4	Decompression, laminectomy	C2-C4	Neurological symptoms improvement 3-month postoperative
Kawano *et al.* (1987)[12]	64 y/F	--	Radicular myopathy Paresthesia of both hand Gait abnormalities Hyperreflexia and hyperesthesia in C7 region	6 months	C3-C4, C5-C6	Decompression, laminectomy	C3-C6	Neurological symptoms improved
Kawano *et al.* (1998)[11]	74 y/F	--	--	--	C4-C6	Decompression, laminectomy	C4-C6	--
Gomez and Chou. (1989)[8]	67 y/F	Osteoarthritis and hypertension Hoffman and Babinski reflex bilaterally	Gait disturbance, neck stiffness, and muscle weakness, clumsiness in both hands	6 months	C3-C5	Decompression, laminectomy	C3-C5	Patient placed in a halo external fixation device for 4 months. Neurological symptoms resolved
Caird *et al.* (1999)[4]	76/F	--	Neck pain Clumsiness of hand Unsteady gait Muscle weakness	3 weeks	C4-C5	Laminectomy	C-5	Discharged 9 days postsurgery
Yamagami *et al.* (2000)[34]	52 y/M	Epileptic seizures	Numbness in bilateral fingers and big toes Gait difficulties Upper extremity muscle weakness	--	C7-T1	Decompression, laminectomy	C4-C6	Rapid dissipation of sensory disturbance and weakness in the upper and lower extremities.
Chen *et al.* (2003)[6]	73 y/F	Hypertension	Nuchal pain with weakness and tingling sensation in both hands Unsteady gait weakened muscles of the left hand	2 months	C5-C6	Decompression, laminectomy	C5-C6	Discharged 10 days postsurgery with remarkable signs
Muthukumar and Karuppaswanny (2003)[23]	1) 70 y/F 2) 55 y/F	1) -- 2) Diabetes Mellitus	1) Weakness of both upper and lower limb 2) Weakness of both upper and lower limb	--	--	1) Decompression, laminectomy 2) Decompression and laminectomy	1) C3-C7 2) C5-C6	1) Ambulatory with support 2) Ambulatory with support
Lin *et al.* (2006)[19]	74 y/F	--	Weakness of the upper extremity Paresthesia of hands Knee swelling and gait difficulties Sensory impairments below C5	--	C3-C6	Decompression and laminectomy	C3-C6	Neurological symptoms improvement after surgery. Pain and paresthesia followed later Improved muscle strength

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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
Mwaka *et al.* (2009)[24]	1) 81 y/F 2) 79 y/M 3) 67 y/F 4) 65 y/M 5) 75 y/F 6) 73 y/F 7) 75 y/M 8) 50 y/M 9) 76 y/M 10) 79 y/M 11) 84 y/M 12) 85 y/F 13) 75 y/F 14) 68 Y/F 15) 76 y/F 16) 74 y/F 17) 59 y/F 18) 71 y/M 19) 79 y/M 20) 86 y/M 21) 70 y/F 22) 58 y/M 23) 59 y/F 24) 78 y/M 25) 77 y/F 26) 76 y/F	1) -- 2) -- 3) -- 4) Hypothyroidism 5) Diabetes Mellitus 6) – 7) Diabetes Mellitus 8) – 9) – 10) – 11) – 12) – 13) Diabetes Mellitus 14) – 15) – 16) – 17) Diabetes Mellitus 18)— 19) Diabetes Mellitus 20) -- 21)-- 22) Diabetes Mellitus 23) Diabetes Mellitus 24)— 25) Diabetes Mellitus 26)--	1) U/L numbness, gait abnormality, motor and sensory deficient, and abnormal reflexes 2) L pain, U/L- numbness, motor weakness and sensory deficient, gait instability, abnormal reflex, and bladder dysfunction 3) U pain, numbness and sensory deficit, gait instability, and arm radicular sign 4)U/L numbness, U motor and sensory deficit, gait instability, abnormal reflex, and arm radicular sign. 5) U/L numbness and sensory deficit, U motor deficit, bladder dysfunction, and abnormal reflex 6) U/L numbness, motor and sensory deficit, U pain, gait instability, bladder dysfunction, abnormal reflex, and arm radicular sign 7) U/L numbness, motor and sensory deficit, U pain, gait instability, and abnormal reflex 8) U pain, numbness and motor deficit 9) U/L numbness, gait abnormality, motor and sensory deficient, and abnormal reflexes 10) U pain and motor deficit, U/L- numbness and sensory deficit, and gait instability. 11) U/L numbness, motor and sensory deficient, abnormal reflexes, gait abnormality, and bladder dysfunction 12) U pain and motor deficit, U/L- numbness and sensory deficit, gait instability, and abnormal reflex. 13) U/L- numbness, motor weakness and sensory deficient, gait instability, abnormal reflex, and bladder dysfunction 14) U/L numbness, U motor and sensory deficit, gait instability, and abnormal reflex 15) U numbness, pain, motor deficit, U/L sensory deficient, abnormal reflexes, and gait abnormality. 16) U/L numbness and sensory deficit, gait instability, and abnormal reflex 17) U/L numbness, gait abnormality, motor and sensory deficient, abnormal reflexes, bladder dysfunction, and arm radicular sign 18) U numbness, pain, motor deficit, sensory deficient, abnormal reflexes, and arm radicular sign 19) U/L numbness, motor and sensory deficit, U pain, gait instability, bladder dysfunction, abnormal reflex, and arm radicular sign 20) U/L- numbness, motor weakness and sensory deficient, gait instability, abnormal reflex, and bladder dysfunction 21) U pain, L sensory deficit, U/L numbness, gait instability, bladder dysfunction, and abnormal reflex 22) U/L numbness, L sensory deficit, U pain, gait instability, bladder dysfunction, and abnormal reflex 23) L pain, U/L numbness and sensory deficit, and gait instability 24) U pain and motor deficit, U/L- numbness and sensory deficit, gait instability, bladder dysfunction, abnormal reflex, and arm radicular sign 25) U/L numbness and sensory deficit, gait instability, and abnormal reflex 26) U/L numbness and sensory deficit, U motor deficit, Gait instability, abnormal reflex, and arm radicular sign	--	1) C4-C6 2) C3-C7 3) C3-C7 4) C2-C4 5) C3-C4 6) C3-C5 7) C3-C7 8) C4-C6 9) C3-C5 10) C3-T1 11) C3-C4 12) C3-C4 13) C4-C6 14) C4-C5 15) C4-C6 16) C6-C7 17) C5-C7 18) C4-T1 19) C3-C5 20) C4-C5 21) C5-C6 22) C4-C5 23) C5-C6 24) C4-C7 25) C4-C6 26) C3-C4	1) Laminoplasty 2) Laminoplasty 3) Laminoplasty 4) Laminoplasty 5) Laminoplasty 6) Laminoplasty 7) Laminoplasty 8) Laminoplasty 9) Laminoplasty 10) Laminoplasty 11) Laminoplasty 12) Laminoplasty 13) Laminoplasty, C5 subtotal 14) Laminoplasty 15) Laminoplasty 16) Laminoplasty 17) Laminoplasty, C5-6 ADIF 18) Laminoplasty 19) Laminoplasty 20) Laminoplasty 21) Laminoplasty 22) Laminoplasty, C4-5 ADIF 23) Laminoplasty 24) Laminoplasty 25) Laminoplasty 26) Laminoplasty	1) C4-C6 2) C3-C7 3) C3-C7 4) C2-C4 5) C3-C4 6) C3-C5 7) C3-C7 8) C4-C6 9) C3-C5 10) C3-T1 11) C3-C4 12) C3-C4 13) C4-C6 14) C4-C5 15) C4-C6 16) C6-C7 17) C5-C7 18) C4-T1 19) C3-C5 20) C4-C5 21) C5-C6 22) C4-C5 23) C5-C6 24) C4-C7 25) C4-C6 26) C3-C4	1) excellent – 0.3 years 2) fair – 1.3 years 3) poor – 5.3 years 4) excellent – 2.1 years 5) excellent – 9.3 years 6) good – 2.3 years 7) good – 0.3 years 8) excellent – 0.5 years 9) good – 9.6 years 10) good – 3.0 years 11) fair – 0.3 years 12) good – 0.3 years 13) fair – 1.5 years 14) good – 7 years 15) good – 0.2 years 16) excellent – 0.3 years 17) good – 0.2 years 18) good – 3.0 years 19) fair – 1.6 years 20) fair – 1.6 years 21) good – 0.8 years 22) good – 0.3 years 23) excellent – 0.3 years 24) good – 0.2 years 25) excellent – 0.2 years 26) good – 0.2 years

(Contd...)

Table 1: *(Continued).*

Authors	Age/sex	Comorbidities	Symptoms	Duration of symptoms before admission	Affected level	Type of surgery	Level of surgery	Outcomes
Sekijima *et al.* (2010)[30]	1) 83 y/F 2) 78 y/M 3) 92 y/F 4) 85 y/F	--	1) Acute posterior neck pain and stiffness 2) Acute posterior neck pain and stiffness 3) Acute posterior neck pain and stiffness 4) Acute posterior neck pain and stiffness	--	1) C3-C7 2) C4 3) C2-C6 4) C5	1) NSAID and prednisone 2) NSAID and prednisone 3) NSAID and prednisone 4) NSAID and prednisone	1) No surgery 2) No surgery 3) No surgery 4) No surgery	1) Symptoms relieved within 1–3 weeks 2) Symptoms relieved within 1–3 weeks 3) Symptoms relieved within 1–3 weeks 4) Symptoms relieved within 1–3 weeks
Kobayashi *et al.* (2016)[15]	70 y/F	--	Neck stiffness – inability to move Neck pain	First admission 14 days - NSAID Second admission - After 2 months, surgery completed within 2 weeks.	C5-C6	Laminectomy	C5-C6	Stabilization within 3 weeks, reduced neck pain. No neck pain post 7 months Complete relief of neck pain post 7 years.
Morino *et al.* (2016)[21]	15 y/M	Coffin-Lowry syndrome	Cervical myelopathy Quadriplegia Spastic tetraplegia Inability to walk, decreased upper extremity activity	2 weeks	C2-T3 YL calcification C1-T1 spinal compression	Decompression, laminectomy	C1-C7	Recovery of upper and lower extremity 8-year follow-up
Kimura *et al.* (2020)[14]	78 y/M	Spinal cord injury - C6	Acute neck pain Cervical Myelopathy Tetraplegia	--	C3-C5	Laminectomy and Laminoplasty	C3 laminectomy C4-C5 laminoplasty	Postoperative uneventful Improvement on 1 year follow up
Liao *et al.* (2021)[18]	65 y/F	Hypertension	Neck pain Bilateral finger numbness left-sided upper extremity weakness	6 months	C4-C5	Laminectomy	C4-C5	--
Lu *et al.* (2021)[20]	1) 70 y/M 2) 85 y/M 3) 59 y/M 4) 80 y/M 5) 66 y/M 6) 72 y/M 7) 86 y/M 8) 79 y/M 9) 87 y/M 10) 73 y/M 11) 78 y/F 12) 70 y/F 13) 77 y/M 14) 81 y/M 15) 67 y/F 16) 81 y/M 17) 78 y/F 18) 77 y/M	1) Diabetes Mellitus 2) Absent 3) Hypertension, Arrhythmia 4) Diabetes Mellitus, Hypertension 5) Hypertension, Hyperuricemia 6) Diabetes Mellitus, Hypertension 7) Hypertension, COPD 8) – 9) Hypertension, COPD 10) Diabetes Mellitus, Hypertension 11) Hypertension, Cardiovascular disease 12) Diabetes Mellitus, Cardiovascular Disease 13) Hypertension, End stage renal disease 14) Hypertension 15) End stage renal disease 16) Diabetes Mellitus 17) Diabetes Mellitus 18) Hypertension	1) Neck pain and myelopathy 2) Myeloradiculopathy 3) Myeloradiculopathy 4) Myelopathy 5) Neck pain and myeloradiculopathy 6) Neck pain and radiculopathy 7) Neck pain and radiculopathy 8) Myelopathy 9) Myeloradiculopathy10) Neck pain and myeloradiculopathy 11) Myelopathy 12) Neck pain and myeloradiculopathy 13) Neck pain and myeloradiculopathy 14) Neck pain and myelopathy 15) Neck pain and myelopathy 16) Myeloradiculopathy 17) Neck pain and myeloradiculopathy 18) Neck pain and radiculopathy	1) 2 months 2) 10 months 3) 3 months 4) 4 months 5) 10 months 6) 3 months 7) 18 months 8) 2 months 9) 2 months 10) 4 months 11) 18 months 12) 24 months 13) 24 months 14) 9 months 15) 15 months 16) 9 months 17) 5 months 18) 12 months	1) C3-C7 2) C5-C7 3) C5-C6 4) C3-C 4, C7-T1 5) C3-C5 6) C2-3, C6-C7 7) C1-C4 8) C2-C5 9) C3-C5 10) C3-C7 11) C4-C6 12) C4-C7 13) C2-C3 14) C2-C4 15) C5-C7 16) C4-C7 17) C4-C6 18) C5-C6	1) Decompression with fusion 2) Decompression 3) Decompression 4) Decompression with fusion 5) Decompression 6) Decompression 7) Decompression 8) Decompression 9) Decompression 10) Decompression 11) Decompression 12) Decompression 13) Decompression 14) Decompression 15) Decompression with fusion 16) Decompression 17) Decompression with fusion 18) Decompression	1) C3-C7 2) C5-C7 3) C5-C6 4) C3-C 4, C7-T1 5) C3-C5 6) C2-3, C6-C7 7) C1-C4 8) C2-C5 9) C3-C5 10) C3-C7 11) C4-C6 12) C4-C7 13) C2-C3 14) C2-C4 15) C5-C7 16) C4-C7 17) C4-C6 18) C5-C6	1) 2–3 2) – 3) 2–3 4) 2–3 5) – 6) 2–3 7) – 8) 2–3 9) 2–3 10) 2–3 11) – 12) 1 13) 1 14) -- 15) – 16) – 17) 2–3 18) – Improvement on discharge based on neural logic.

U/L: Upper extremity, Lower extremity, CPPD: Calcium pyrophosphate dehydrate, CLF: Cervical ligamentum flavum

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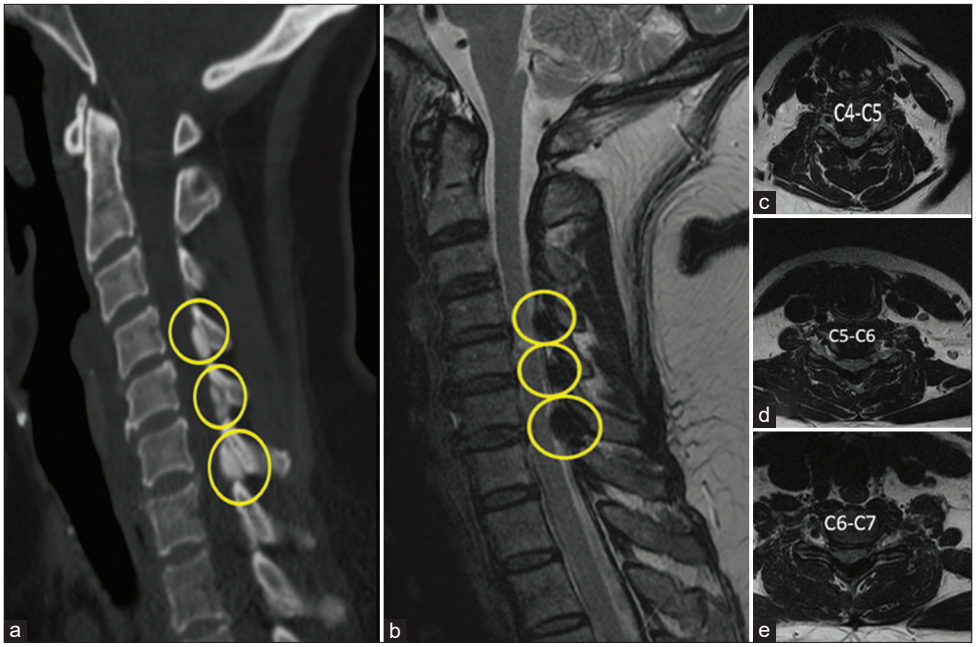

Figure 1: Sagittal Computed tomography (a), T2-weighted Magnetic resonance imaging (b), and (c,d,e) Axial T2-weighted images of calcium pyrophosphate dehydrate (CPPD) deposit disease in the cervical ligamentum flavum (CLF) of a 60-year-old female with cervical myelopathy presenting with balance and gait abnormalities. Sagittal yellow images circle (a,b) denotes a CPPD compression lesion in C4-C5, C5-C6, and C6-C7 CLF lamina. Axial images present spinal canal stenosis.

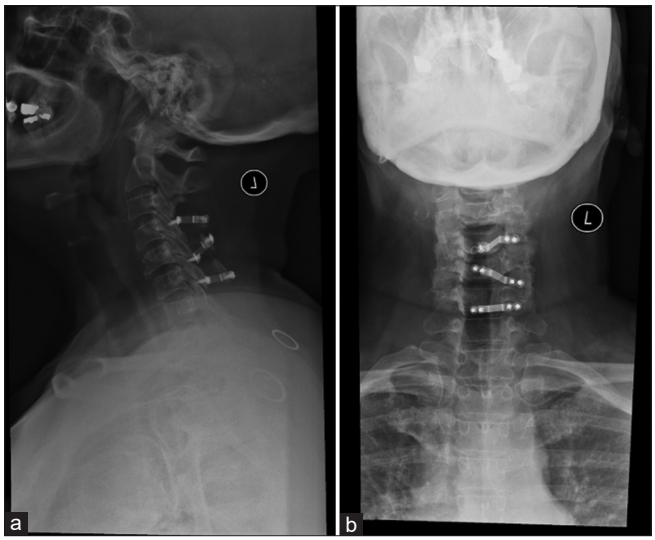

Figure 2: The 60-year-old female underwent a C4-C6 laminoplasty and C3 and C7 partial laminectomy with instrumentation. Lateral (a) and anteroposterior (b) radiographic demonstrating the laminoplasty and partial laminectomy taken post surgery. Patient's symptoms were resolved.

However, we found similar results as Richette *et al*. in 2009 with similar prevalence between men and women [Table 2].[28]

Although the direct cause of pseudogout is still unclear, some reported that metabolic risk factors for CPPD deposit

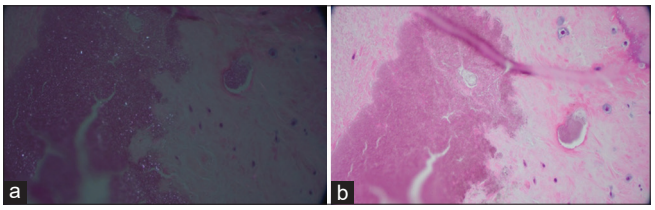

Figure 3: (a) Polarized light microscopy shows calcium pyrophosphate dehydrate (CPPD) deposit within a degenerated cervical ligamentum flavum (CLF). (b) CPPD deposit within a degenerative CLF without polarized light.

disease in the CLF are hyperthyroidism, hypothyroidism, hyperparathyroidism, osteoarthritis, diabetes mellitus, arthrosclerosis, hypertension and hemochromatosis, Wilson's disease, hypophosphatasia, hypomagnesemia, and loop diuretics use.[8,18,23,24] Hyperparathyroidism, hemochromatosis, hypothyroidism, and hypomagnesium have the strongest association with CPPD deposition in the CLF.[31] In addition, CPPD deposition can also be associated with trauma and surgery.[14] In our review [Table 3], we found the comorbidities most associated with CPPD deposition in the CLF were diabetes mellitus and hypertension.[24] 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.

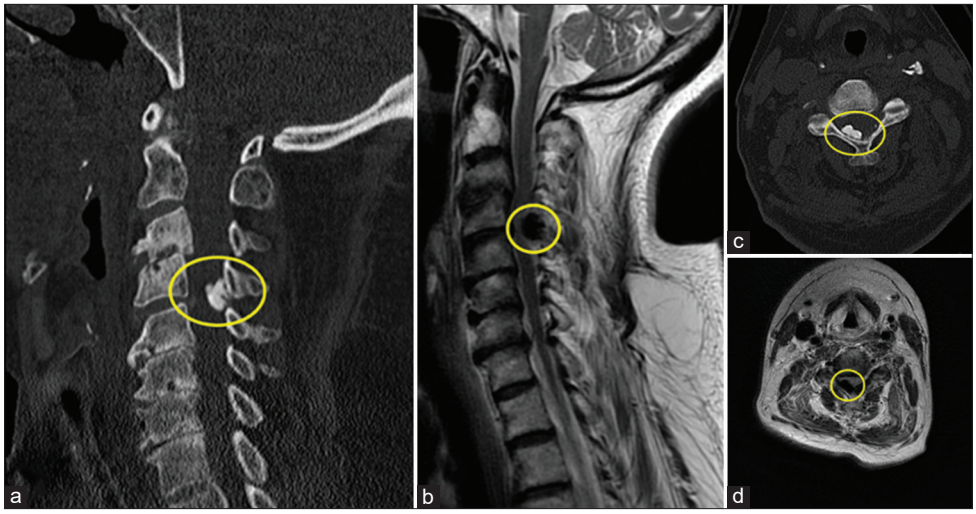

Figure 4: Sagittal computed tomography (CT) (a), T2-weighted magnetic resonance imaging (b), axial CT (c), and T2-weighted (d) images of calcium pyrophosphate dehydrate (CPPD) deposit disease in the cervical ligamentum flavum (CLF) of a 70-year-old female with cervical myelopathy presenting with balance and gait abnormalities experienced falls. The yellow circles (a,b,c,d) denotes a CPPD compression lesion in C4-C5 CLF lamina.

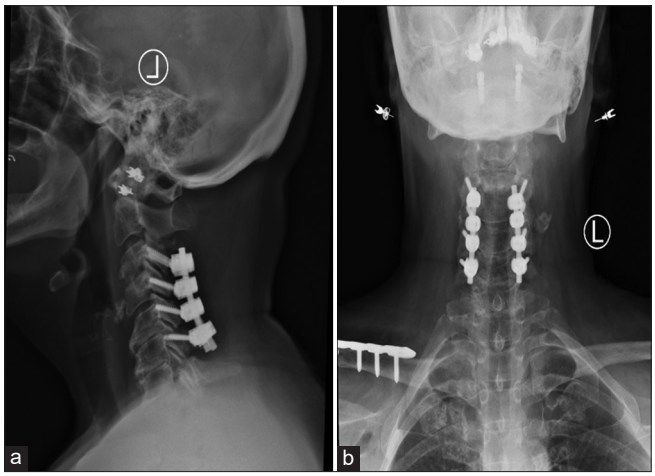

Figure 5: A 70-year-old female underwent a C3-C6 posterior spinal fusion (PSF) and a C3-C6 laminectomy with instrumentation. Lateral (a) and anteroposterior (b) radiographs demonstrate the PSF and laminectomy post surgery.

PATHOLOGY/PATHOPHYSIOLOGY

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.[20] The thickness of the ligamentum flavum increases with age and accumulation of mechanical stress which is associated with increased fibrosis and decreased elastic fibers.[29] Transforming growth factors-beta (TGF-*B*) may stimulate fibrosis particularly during early hypertrophy.[29] 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.[6]

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.[5,31] Sporadic acquisition is most common while genes localized on chromosome 5p are shown to be responsible for familiar inheritance.[27] 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.[6] Kimura *et al*. 2020[14] 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.[33] Wide amorphous fibrotic areas with a reduced number of elastic fibers and increased collagenous tissue were frequently observed in pathologic CLF.[24] Chondrocytes were found around the deposits of calcium scattered among the matrix of the ruptured elastic fiber bundles.[6] Furthermore, small blood vessel was shown to proliferate within the periphery of the calcified lesion.[24] 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.[24] Phagocytosis of polymorphonuclear leukocytes and release of inflammatory factors then lead to acute inflammation at the ligamentum flavum.[6]

CPPD is frequently associated with generalized collagen degeneration.[15] 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.[1] The C5 segment shows the highest dynamic stress in the cervical region with the elastic tissue most prone to degeneration.[6,11,12,20] This may be the result of the relatively thin and highly elastic ligamentum flavum of the cervical spine.[20] 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 [Table 4].[20] Repetitive stretch, trauma, and advanced age are contributing factors to crystal deposition in the cervical spine.[6]

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.[10,25] Symptoms can vary from neck pain to myelopathic symptoms such as numbness of upper extremity, gait abnormalities, and bladder dysfunction.[20] CPPD in the CLF creates a pathological lesion which compresses the cervical spinal cord dorsally leading to a more pronounced decrease in sensation.[24] 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 [Table 5]. It is important to note that 10–20% of patients do not present with any symptoms.[10,31] 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.[20,33] Differentiation of these two disorders is critical in making an appropriate diagnosis and the implementation of appropriate treatment.[33] CPPD primarily deposits in the cervical spine while OLF has no common location. CPPD typically affects multiple levels while OLF most often affects a single segment.[19,31]

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.[16,20] CPPD lesions have a nodular-type appearance instead of a beak-like or mound-like appearance which is seen in OLF.[9,19] 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 side.[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,[17] patients with CPPD have normal uric acid laboratory values.[13,21,25] Gout is therefore more associated with monosodium urate monohydrate crystals in patients with elevated serum urate concentration.[31] 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].[17]

IMAGING

Sagittal CT [Figures 1a and 4a] of the cervical spine is the most effective way to diagnose CPPD in the CLF.[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.[2,6] MRI detects the level of spinal cord compression and other soft-tissue changes.[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.[32]

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[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.[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.[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.[6,30] Some patients have experienced symptom relief within 1–3 weeks of implementing conservative methods.[30] Even so, symptoms may recur and worsen rendering non-operative and conservative methods ineffective long-term.[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].[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.[20] Decompression at those levels often results in the return of neurological function.[34] However, intraoperative complications such as dural tears can occur due to CPPD lesions adherence to the dura matter.[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.[14] Depending on the degree and length of time, the spinal cord was compressed there may be irreversible damage that will persist despite decompression.[10] Furthermore, patients should be monitored overtime to identify CPPD deposition in other areas of the ligamentum flavum.[20]

Early surgical treatment produces better long-term outcome and return of neurological function.[4,10] Patients with symptoms lasting under a 5-month duration showed the greatest and earliest improvement in neurological function after a laminectomy.[20,25] In contrast, patients with symptoms lasting over 24 months demonstrated an inability to recover to presymptomatic levels.[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. CPPD's 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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Ehioghae M, Lawlor MC, Mesfin A. Calcium pyrophosphate dihydrate of the ligamentum flavum in the cervical spine – A review of the literature. Surg Neurol Int 2022;13:470.