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REVIEW

Lumbar Spinal Involvement in Calcium Pyrophosphate Dihydrate Disease: A Systematic Literature Review

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Background: Calcium-pyrophosphate-dihydrate-disease (CPPD) is a crystal-induced arthropathy. The lumbar-spinal involvement is rare and often under-diagnosed. This study aimed to report the case of a lumbar spine CPPD involvement and to perform a systematic review of clinical, imaging features of lumbar involvement in CPPD patients, and treatments that have been implemented.

Methods: This systematic review was conducted in accordance with the Preferred-Reporting-Items-for-Systematic-Reviews and Meta-Analyses (PRISMA) guidelines.

Results: One hundred and sixty-seven articles met the search criteria using electronic databases searches. We retained 28 articles (20 case reports, 2 case series, 1 family survey, 4 retrospective studies, and 1 prospective study) involving a total of 62 patients. The age ranged between 39 and 89 years old. Among patients with lumbar spine CPPD, 32 were women. The duration of symptoms varied between one day and 8 years. The affection has been discovered during back pain in most cases. In 5 studies, the diagnosis was made on histological specimens of patients operated on for another pathology. X-ray showed calcifications in 2 cases. CT-scan detected calcium deposit in 7 cases. MRI showed lesions going from the increased signal of the disk, to calcified or not-cystic lesion of the facet joints, an intramedullary mass mimicking a schwannoma. Histological examination established the diagnosis of CPPD in 21 patients in all studies. Medical treatment included NSAIDs, Colchicine, Interleukin-1-receptor-antagonist, and antibiotics. Surgery was performed on 13 patients and allowed to establish the histological diagnosis.

Conclusion: In the case of inflammatory back pain in elderly subjects, without an infectious gateway, diagnosis of CPPD should be considered, especially for patients with a history of spinal surgery or degenerative radiography changes. CT scan is more sensitive than conventional radiographs. The discovertebral biopsy is the Gold-Standard and should be performed whenever the diagnosis was uncertain. Treatment includes the medical and surgical components.

Keywords: chondrocalcinosis, calcium pyrophosphate dihydrate disease, spine, radiculopathy, sciatica

Background

Calcium pyrophosphate dihydrate disease (CPPD) is a pathology defined by a deposit of crystals of calcium pyrophosphate dihydrate in the joints. Spinal CPPD is present in different clinical pictures depending on its location. The location of the cervical spine is best known as crowned dens syndrome, but the locations can affect all parts of the spine. Clinical presentation could be acute, subacute, or chronic spinal pain. It can even mimic infectious spondylodiscitis in its spinal form. But often, it is of radiological discovery, where the deposition of CPPD crystals occurs within the hyaline cartilage and especially within fibrocartilages.[1] Although CPPD has several radiographic features in common with primary osteoarthritis, the axial location of the calcifications is an important criterion of distinction.[2]

Thus, the clinical pictures can be diverse and mislead the clinician in his diagnosis. It is therefore important to know the different presentations of this pathology.

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This study aimed to report the case of a lumbar spine CPPD location and to review clinical, imaging features of lumbar involvement in CPPD patients, and treatments that have been implemented.

Case Report

Written informed consent has been provided and signed by the patient to have the case details and any accompanying images published. A 73-year-old patient, with a history of multiple comorbidities, presented with chronic knee and shoulders pain. X-rays revealed calcifications of the cartilages and entheses in the knees, shoulders, and pelvis, as well as symphysitis. We made the diagnosis of CPPD and the patient was put on colchicine for 15 days with clinical improvement. Six months later, she complained of non-inflammatory L5 sciatica associated with neuropathic pain (DN4 score was 6/10), without signs of impingement. Plain radiography showed levoscoliosis and nonspecific degenerative findings (disc space narrowing, osteophyte formation). Lumbar CT scan disclosed calcifications of the interspinous ligaments, yellow ligament, anterior and posterior disc calcifications, and a focal median and left paramedian protrusion at the L5-S1 level, with cranial migration of 9mm (Figures 1–3). The patient was put on colchicine (1mg daily) and rehabilitation. Symptoms were decreasing and pain relief was reported. At 36 months of follow-up, she still complained of sciatica flare-ups.

Literature Review

Methods

Database and Search Strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

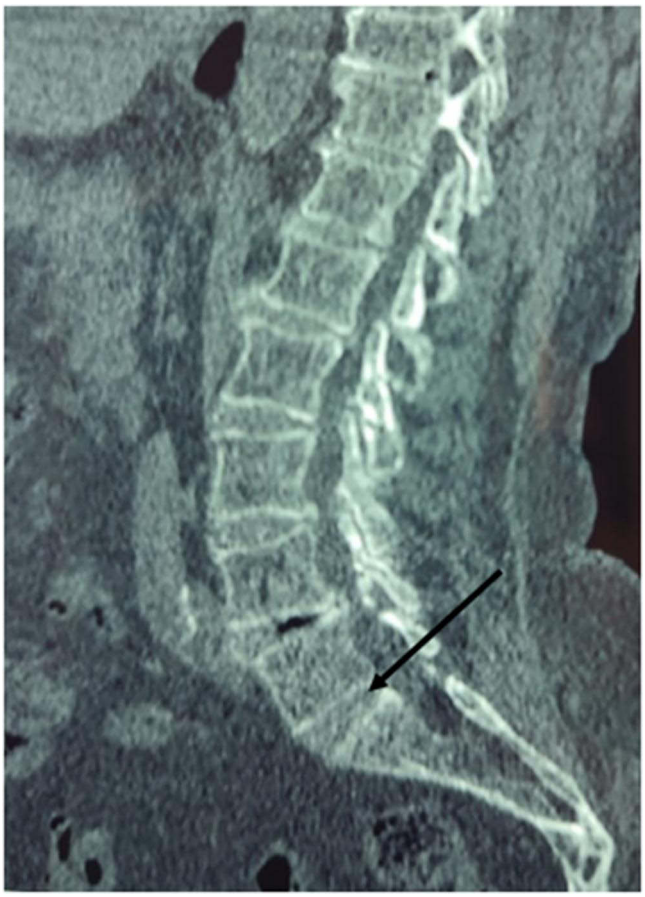

Figure 1 A CT-scan sagittal image shows linear calcification into the L3-L4, L4-L5 and L5-S1 (Arrow) intervertebral discs.

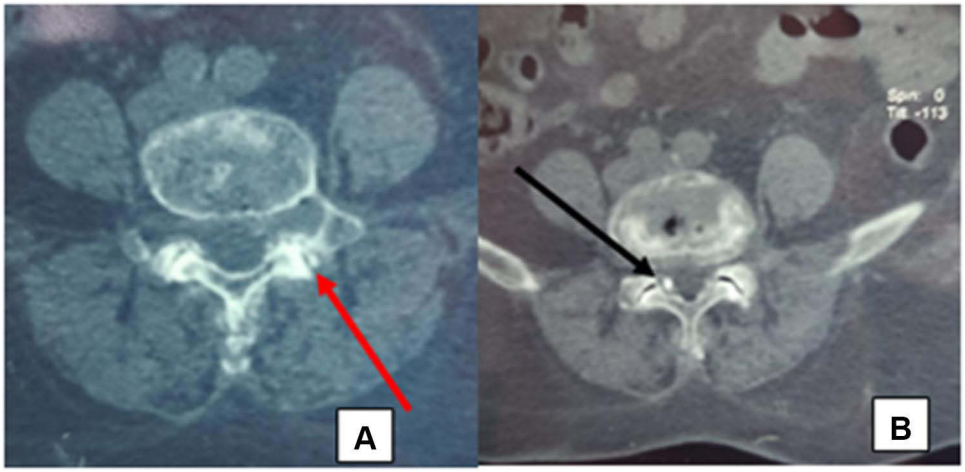

Figure 2 Axial CT-scan image of the lumbar spine, exhibiting calcification of the interapophyseal joint cartilage (Red Arrow) in (**A**) and ligamentum flavum (Black Arrow) in (**B**).

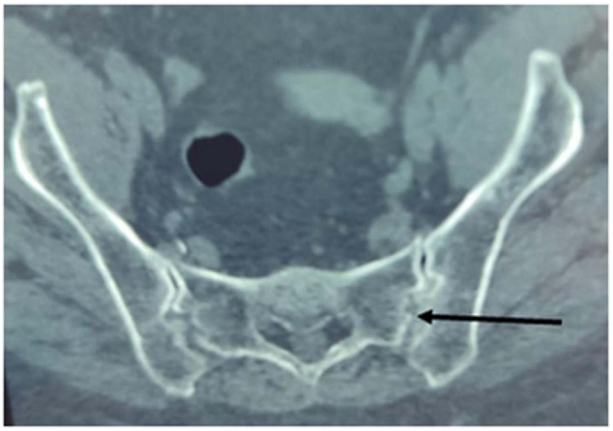

Figure 3 AxialCT-scan image of the pelvis showing linear bilateral calcification of the sacroiliac joint (Head arrow).

The search of articles was performed in PubMed, Google Scholar, Medline, Scopus, and Cochrane library databases. The following keywords were used: ("Chondrocalcinosis" OR "Calcium Pyrophosphate Dihydrate Disease") AND ("Spine" OR "Osteoarthritis, Spine" OR "radiculopathy" OR "sciatica" OR "lumbar vertebrae"). Keywords referred to medical subject heading (MeSH). All references list of the retained papers were also screened manually for additional eligible studies. Titles, abstracts, and full reports of the identified articles were systematically screened.

Study Selection Criteria

Papers screened for eligibility were case reports, meta-analysis, systematic reviews, letters, cross-sectional, prospective and retrospective studies published in English or French that incorporate CPPD of the lumbar spine. Articles that treated other joints, cervical and thoracic spine were not included. Studies of more than 20 years were excluded.

Data Extraction and Quality Assessment

All selected articles were reviewed by two authors. Each article was analyzed through a critical reading platform: Fichas de LecturaCritica 3.0 to determine whether it fulfilled or not validity criteria. All data were extracted using a standardized template: title, author, type of the study, year of publication, and study population. For case reports, clinical presentation, imaging, biological findings, and treatment were mentioned. Only studies rated "High" or "Average" were selected. For cohort studies, we used the Newcastle Ottawa Scale (NOS). For case series and case reports, we used the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports.

Statistical Analysis

We used descriptive statistics to report data.

Results

Flow Chart of the Study

A total of 167 articles met the search criteria using electronic databases searches (PubMed, Google Scholar, Scopus, and Cochrane library databases manual research, references lists). We identified 110 studies after screening titles and abstracts and removing duplicates. After excluding the cervical and thoracic location and assessing the value quality of the studies, we retained 28 articles (20 case reports, 2 case series, 1 family survey, 4 retrospective studies, and 1 a prospective study) involving totally 62 patients. Among the studies selected, 4 screening studies with asymptomatic patients were performed on histological specimens (Figure 4).[3–6] Detailed characteristics of all studies included are summarized in Table 1.

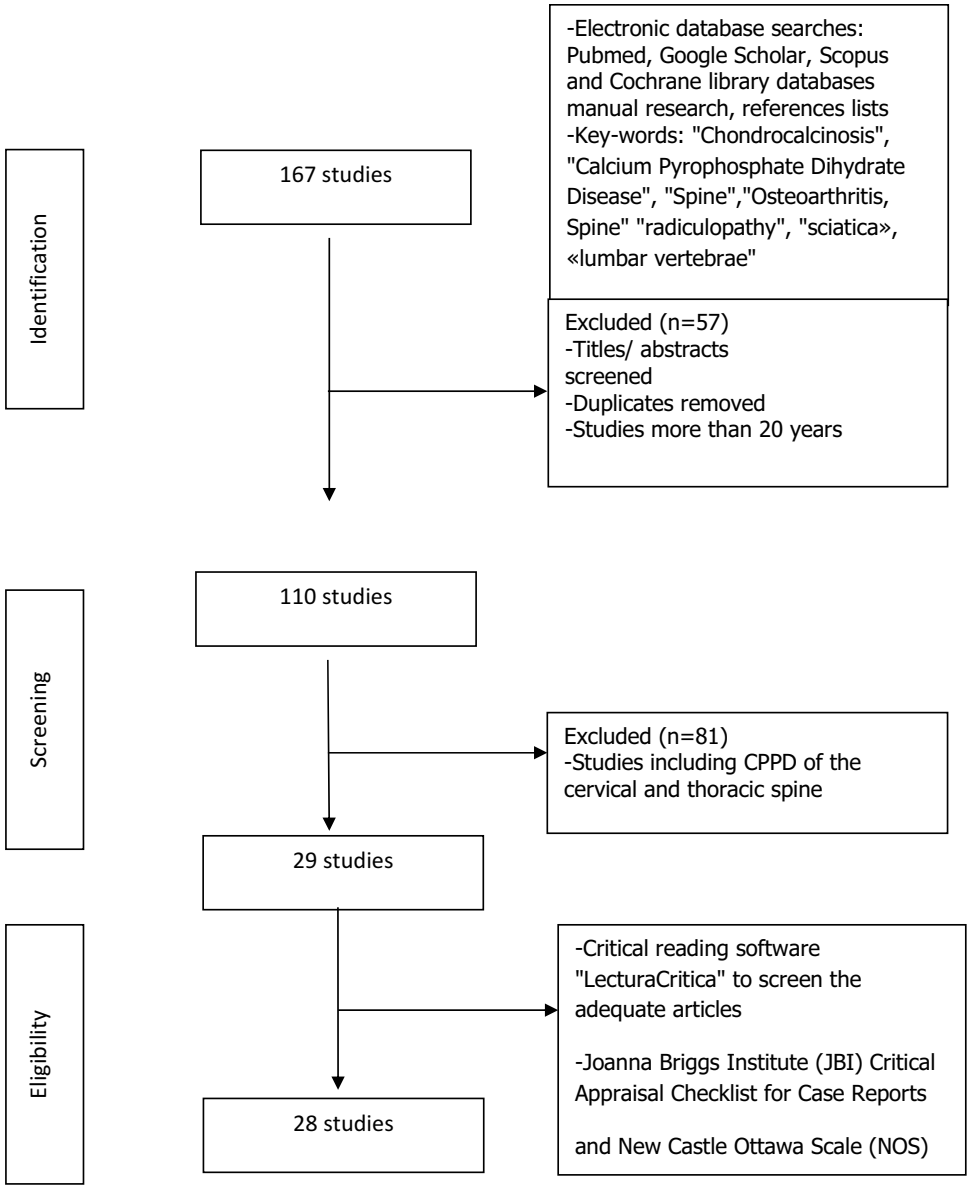

Figure 4 Flow chart of the study.

Table 1 Overview of the Studies on Lumber CPPD

Reference	Year	Study Design	Clinical Features	Diagnostic Method	Outcomes	Treatment	Follow-Up
Petit H, Marcellin L, Chatelus E. LumbarSpineChondrocalcinosis. J Rheumatol2017;44:1288–9.[7]	2017	Case report (1)	Woman, 70 years inflammatory low back pain for a month Suspicion of spondylodiscitis Low grade fever	MRI Histology (biopsy)	Septic localization with T2 short-tau inversion recovery hypersignal on the left lumbar facet joints L3–L4 and L4–L5 Direct exam: no microorganism Culture: sterile at 48 h Histo: basophilic material including numerous rhomboidal crystals birefringent in polarized light (CPPD)	NSAIDs	Improvement
Reis GF, Perry A. A 67-Year-Old Man with a Lumbar Spine Lesion: Correspondence. Brain Pathology 2014;24:547–8.[24]	2014	Case report (1)	Man, 67 years History of laminectomy for lombar spinal stenosis Low progressive back pain for 1 year	X-Ray MRI Histology (tumor resection)	Lumbar levoscoliosis, multilevel degenerative lumbar disease and lumbar lordosis with normal pelvic tilt Multilevel degenerative disc disease and an incidental intradural, intramedullary mass at L1–L2: suspicion of schwannoma The crystals demonstrated positive birefringence on polarizable light	Tumor resection	Not mentioned
Baty V, Prost B, Jouvet A, Laurent J, Vallée B. Acute spinal cord compression and calcium pyrophosphate depositiondisease. Journal of Neurosurgery:Spine 2003;99:240.[8]	2003	Case report (1)	Woman, 39 years History of b-thalassemia major and secondary hemochromatosis 1-month low back pain	X-Ray MRI Histopathology	Calcifications of the lower thoracic and the lumbar discs Marked compression of the spinal cord related to an L1–2 disc herniation Degenerative and calcifiedlesions	Bilateral decompression and fusion	Good results
Vincent Grobost et al. Axial calcium pyrophosphate dihydrate deposition disease revealed by recurrent sterile spondylodiscitis and epidural abscess. Joint Bone Spine 2014;81:180–2.[22]	2013	Case report (1)	Man, 85 years History of prostate cancer and sterile spondylodiscitis in 2008, CPPD of the knee in 2008 Acute back pain	MRI CT scan CRP Histopathology	Spondylodiscitis L4L5, epidural abcess, gadolinum-enhanced signal in L1-L2 and L4-L5 zygapohysal joints Calcium deposit in L2-L3 and L4-L5 zygapophysal joints and intervertebral lumbar disks 60mg/L Sterile culture, CPPD	Colchicine 1 mg/j	Clinical signs improved in 72h CRP back to normal
Gadgil AA, Eisenstein SM, Darby A, Cassar Pullicino V. Bilateral Symptomatic Synovial Cysts of the Lumbar Spine Caused by Calcium Pyrophosphate Deposition Disease: A Case Report. Spine2002;27:E428–31.[9]	2002	Case report (1)	Woman, 67 years Low back pain Disease duration: 8 years	CT scan MRI Histopath	Large calcification cystic lesion above the right L4-L5 disc compressing the spine development of a new calcified cystic lesion extending from the left L4–L5 facet joint through the ligamentum flavum and compressing the theca and the left L5 nerve root posterolaterally. **Fibrous tissue** with synovial lining, CPPD crystals	Surgical decompression	Recurrence MRI: new calcified cystic lesion Second surgery Resolution of symptoms

(*Continued*)

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Table 1 (Continued).

Reference	Year	Study Design	Clinical Features	Diagnostic Method	Outcomes	Treatment	Follow-Up
Ujihara T, Yamamoto K, Kitaura T, Katanami Y, Kutsuna S, TakeshitaN, et al. Calcium Pyrophosphate Deposition Disease Involving a Lumbar Facet Joint Following Urinary Tract Infection. Intern Med 2019;58:1787–9.[10]	2019	Case report (1)	Woman, 75 years E. Coli urinary infection Fever and acute low back pain at J8 of Levofloxacin History of kideny stones	X-Ray MRI	Cartilage calcification of the wrist, knee, shoulder Liquid retention at the lumbar facet joint (L4-L5) without findings compatible with discitis or vertebral osteomyelitis	NSAIDs	Pain and fever improved No recurrence
Mikhael MM, Chioffe MA, Shapiro GS. Calcium Pyrophosphate Dihydrate Crystal Deposition Disease (Pseudogout) of Lumbar Spine Mimicking Osteomyelitis-Discitis With Epidural Phlegmon n.d.:4.[26]	2013	Case report (1)	Man, 60 years History of Parkinson L4-L5 laminectomy new-onset severe low back pain and bilateral leg pain. Returned 2 months later with worsening bilateral leg pain (right more than left), dorsiflexion weakness, and diminished sensation along the lateral and plantar right foot.	MRI Repeated MRI CT scan Percutaneous-tissue biopsy Histopath (surgery)	Increased signal within the L5–S1 intervertebral disk and the endplates of the L5 and S1 vertebrae on the T1- and T2-weighted sequences Interval increase in the T2 signal within the L5–S1 intervertebral disk and markedly enhancing soft-tissue in the epidural space on the T1 -weighted postcontrast sequences at the L5–S1 level Progressive erosive changes in the L5 vertebral body when compared to a CT scan from the first crisis Non contributive Negative culture Chalky white material CPPD	Surgery	
Bin Mohamed Namazie MR, Fosbender MR. Calcium Pyrophosphate Dihydrate Crystal Deposition of Multiple Lumbar Facet Joints: A Case Report. J Orthop Surg (Hong Kong) 2012;20:254–6.[11]	2012	Case report (1)	Woman, 69 years One-year history of low back pain that had increased over the past 2 months	Neurological Examination Inflammatory markers X ray CT scan MRI Histology (open spinal decompression)	Normal slightly raised, with a C-reactive protein level of 15 mg/l (reference range, 0–4 mg/l) and erythrocyte sedimentation rate of 46 mm/h (reference range, 0–20 mm/h). Hypertrophic degenerative changes of the facet joints of L4-L5 and L5-S1, and a grade-one spondylolisthesis of L4 on L5. Large calcified mass in the left side of the spinal canal of L4-L5 extending through the left intervertebral foramen, with posterolateral disc protrusion Calcification extended from the left L4-L5 facet joint to the medial aspect of the L5-S1intervertebral foramen.densely calcified cyst (4 cm in diameter) in the left L4-L5 facet joint extending into the spinal canal and intervertebral foramen. In the L5-S1 facet joint, another calcified cyst was noted Presence of positively birefringent crystals on polarised light microscopy.	Open spinal decompression	No intra- or post-operative complications. At one-year follow-up, the radicular symptoms and back pain had resolved completely, and the patient was neurologically intact.

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Lee J, Cho K-T, Kim E-J. Cauda Equina Syndrome Caused by Pseudogout Involving the Lumbar Intervertebral Disc. J Korean Med Sci 2012;27:1591.[29]	2012	Case report (1)	Man, 59 years History: uncomplicated L4-L5 discectomy 15 yr prior, and had a 2-month history of LBP, which was being managed conservatively Clinical features: Severe lumbago and progressive neurological symptoms, including right-sided foot drop, numbness at both legs, and residual urine sensation. numbness in both legs, weakness on his right leg, urinary retention, and a worsening limping gait	MRI CT scan Histopath	Extradural heterogeneous mass-like lesion in the anterior epidural space at the intervertebral disc space of L4-L5, which was severely compressing the thecal sac A patchy calcified lesion biopsy of the intervertebral disc and epidural mass-like lesion was determined to be CPPD deposits consistent with pseudogout	Emergent surgery	symptoms of saddle hypesthesia and numbness on both legs were improved markedly
Lam H, Cheung K, Law S, Fung K. Crystal Arthropathy of the Lumbar Spine: A Report of 4 Cases. J OrthopSurg (Hong Kong) 2007;15:94–101.[18]	*2007*	Case series (4) 4 crystal arthropathy 2 CPPD	Woman, 79 years 2-week history of increasing numbness in both her lower limbs. on-andoff back pain, aggravated by walking, for years Woman, 72 History: leftsided L5 hemi-laminectomy for leg numbness Stomach and cervical tumours surgically removed many years previously Clinical features: bilateral buttock pain associated with lower limb numbness on walking which developed one year after the spinal operation	X-Ray MRI A diagnosis of spinal stenosis with cauda equina syndrome was made. Histopath X-Ray CT scan MRI Histopath	Degenerative changes with a collapsed L4 A marked stenosis at the L3/4 level with a hypertrophic ligamentum flavum Fibrous tissue mingled with multiple aggregates of rhomboid crystals (CPPD) Old collapse fractures of L1 and L5 old osteoporotic collapse fractures of L1 and L5 Marked spinal stenosis with compression of the thecal sac at the L4/5 level caused by the combination of posterior bony protrusion from the collapsed L5 vertebral body, L4/5 disc bulging and L4/5 facet joint hypertrophy The chalky material was also found in the epidural space, encasing the right L5 nerve root Positively birefringent crystals of calcium pyrophosphate	Emergency L3 laminectomy surgical exploration: ligamentum flavum was found to have been removed on the left side and was swollen and hypertrophied on the right side at the L4/5 level, due to deposition of whitish chalky material	The numbness over both lower limbs improved Cladication improved

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Table 1 (Continued).

Reference	Year	Study Design	Clinical Features	Diagnostic Method	Outcomes	Treatment	Follow-Up
Mahmud T, Basu D, Dyson PHP. Crystal arthropathy of the lumbar spine: A SERIES OF SIX CASES AND A REVIEW OF THE LITERATURE. The Journal of Bone and Joint Surgery British Volume 2005;87-B:513–7.[19]	2005	Case series(6) 6 crystal arthropathy 3 CPPD	Woman, 70 years one-month history of pain over the lateral aspect of her right calf radiating to her foot. weakness of extensor hallucis longus on the right side Man, 81 six-month history of worsening claudication. Man, 79 a three-month history of severe right sciatic pain instrumented posterolateral fusion and decompression for lytic spondylolisthesis at the L4/5 level ten years earlier with good relief of symptoms.	X-Ray MRI Histopath MRI Histopath MRI Histopath	Degenerative changes with no specific features Degenerative disc and facet disease and showed a large right-sided synovial cyst measuring 7 mm x 8 mm arising from the right L4/5 facet joint causing considerable thecal and nerve-root compression. Positively birefringent, short blunt crystals, (CPPD) Severe stenosis of the canal due to a combination of structural deformity and enlargement of a facet cyst (Figure 3). The peri-articular spinal tissue was found to contain CPPD crystals when examined under polarised light. Stenosis at L2/3 and L3/4 above the previous fusion which was intact CPPD	Right L4/5 spinal decompression and excision of the synovial cyst through a wide fenestration The cyst was noted to contain tophaceous material Epidural injection of steroids: failed Surgical decompression: extensive synovial cyst containing tophaceous material and surrounding the right L4 nerve root	Unventful recovery with resolution of the neurological symptoms
Gruber HE, Norton HJ, Sun Y, Hanley EN. Crystal deposits in the human intervertebral disc: implications for disc degeneration. The Spine Journal 2007;7:444–50[3]	2007	Prospective study	211 patients Herniated discs, degenerative discs, recurrent disc herniation Age	Incidence of CPDD: 14.69% Grade II: mean age 35 ±11.8 Grade III: mean age 41.9 ±8.8 Grade IV: mean age 59.7 ±11.5	Multiple, large masses of crystals in annulus large numbers of crystals of rectilinear shape with high birefringence long crystalline structures Small, single triclinic crystals within small vacuoles Other cases presented with a much more irregular, amorphous deposition pattern		

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Pakzad K, Yang YJ, Ambrose JL, Landas SK. Diagnosis of Calcium Pyrophosphate Dihydrate Deposition Disease by Fine Needle Aspiration Biopsy. Acta Cytologica2002;46:46–9[25]	2002	Case report	Man, 73 years Medical history of prostate carcinoma, coronary arterydisease, diabetes mellitus, hypothyroidism,"gout", osteoarthritis and hypertension. Lower back pain and low grade fever.Blood culture positive for Streptococcus Treated by intravenous (IV) cephazolin for two weeks and discharged on cephradine.	MRI Repeated MRI (CT)–guided FNAB of the lumbar lesion Repeated MRI Repeat CT-guided FNAB CT guided FNAB using a 23-gauge needle	Increased signal consistent with an inflammation. Extensive osteomyelitis and discitis involving the L3–L4 intervertebral disc as well as the adjacent L3 and L4 vertebral bodies, with soft tissue extension. No microorganisms grew in the culture. Further loss of bone substance and a small abcess at the L3–L4 disc level. No microorganism –> IV ceftriaxone, and his symptoms gradually and significantly improved in the ensuing three months. These crystals presented as translucent, negative images in the bluestained background	Antibiotics	Improvment
Amouzougan A, Vassal F, Peoc'h M, Marotte H, Thomas T. Calcium Pyrophosphate Deposition Disease Arthropathy–Related Sciatica. Arthritis Rheumatol2019;71:2099–2099[12]	2019	Case report	Woman, 65 year old Severe sciatica of S1 topography related to an intra canal conflict History of asymptomatic willbrandt disease	MRIT1 weighted, T2 weighted and post contrast T1 weighted fast suppressed: Surgical macroscopic observation Histological analysis Wrist and knees X rays Retrospective study of CT images	Neural lesion compatible with a schwannoma Green yellow cyst of articular origin Zygapophyseal arthritis with CPPD crystals and hemosiderin deposit Multiple CPPD crystaldepositsL5 S1 CPPD lesions	Surgery	Improved
Wendling D, Martin M, Guillot X, Prati C. Interspinous bursitis and chondrocalcinosis. Joint Bone Spine 2012;79:516.[13]	2012	Image	Woman, 69 years inflammatory low back andbuttock pain since two weeks	Biology Lumbar X ray X ray of the wrist and knee MRI CT scan with sagittal reconstruction	Elevated CRP Non informative Chondrocalcinosis Gadolinium-enhanced T1 sequence hypersignal calcified deposits in the intervertebral disc as well as in the interspinous space (microcristalline interspinous bursitis)	NSAIDs	Improved CRP returned to normal

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Table 1 (Continued).

Reference	Year	Study Design	Clinical Features	Diagnostic Method	Outcomes	Treatment	Follow-Up
Fujishiro T, Nabeshima Y, Yasui S, Fujita I, Yoshiya S, Fujii H. Pseudogout Attack of the Lumbar Facet Joint: A Case Report: Spine 2002;27:E396–8.[14]	2002	Case report	Woman, 71 years History of diabetes and hypertension progressive pain and swelling in her left knee on ambulation. 2 days later, acute low back and left buttock pain and a fever of 38.6 C no objective neurologicdeficit	X ray Joint aspiration Laboratory parameters X ray MRI axial Aspiration of the left L4–L5 facet joint polarized light microscopy	No CPPD Identification of typical calcium pyrophosphate crystals in normal hemoglobin levels, normal liver function test results, and normal results on uric acid, calcium, phosphorus, and urine analyses ESR= 51, CRP=11,9 Slight intervertebral disc degeneration and moderate facet joint degeneration at the L4–L5 level joint effusion at the level of the bilateral L4–L5 facet joint Culture: negative monoclinic or triclinic intracellular crystals with a positive birefringence.	Joint aspiration	Imrpovedafter aspiration Complete resolution after 8 months follow up Control CT scan: osteoarthritis of the bilateral L4–L5 facet joints without CPPD
Cameron CR, Burgess CD. Recurrent back pain and fevers. Medical Journal of Australia 2007;186:208–9.[15]	2007	Case report	Woman, 78 year old acute onset of severe lumbar back pain radiating down both posterior thighs, bilateral leg weakness, and paraesthesiae of the feet on getting out of bed that morning. power was reduced in all movements of the knee and ankle Reflex testing showed reduced knee jerks, absent ankle jerks and downgoing plantar reflexes. Although anal tone was reduced 2003: diagnosedwithlumbardiscitis	MRI scan Cerebrospinal fluid (CSF) aspirated under computed tomography (CT) guidance Histopath	50% spinal canal compromise, at multiple levels, due to marked osteophytosis of the facet joints, ligamentum flavum hypertrophy and spondylolisthesis; the spinal cord was normal, but an abnormal signal was detected in the L3/L4 disc Sterile Calcium pyrophosphate crystals were present		
Moshrif A, Laredo JD, Bassiouni H, Abdelkareem M, Richette P, Rigon MR, et al. Seminars in Arthritis and Rheumatism 2019;48:1113–26[20]	2018	Case series (37)	152 CPPD patients in the rheumatology department of Lariboisiere 37 spinal location Cervical and lumbar+++ Mean age: 78 years	CT scan more sensitive than plain radiographs			

Ariyawatkul T, Pichaisak W, Chavasiri C, Vamvanij V, Wilartratsami S, Luksanapruksa P. Asian Spine J 2019;13:1001–9.[4]	2019	Retrospective study	Thirty-four patients were enrolled, with 18 patients being allocated to the SCPPD group and 16 being allocated to the non- CPPD group.		Surgical intervention resulted in good clinical outcomes in SCPPD patients. As per our findings, total removal of CPPD-involved tissue is unnecessary.		
Loizidis G, Stern J, Baker JF. When Calcium Pyrophosphate Deposition Disease Masquerades as Spinal Infection: JCR: Journal of Clinical Rheumatology 2019;25:e118–22.[21]	2018	Case report	55-year-old woman with no prior CPPD and medical history of poorly controlled diabetes mellitus (type 1) a chief complaint of lower back pain and leg pai	MRI Repeated MRI Surgery for L2–L3 laminectomies, discectomy Histopath (surgery)	Osteomyelitis and discitis of L2–L3 worsening discitis-osteomyelitis with moderate spinal canal stenosis crystalline deposits in the ligamentum flavumand the intervertebral disc compatible with CPPD.	6 weeks of empiric ceftriaxone and vancomycin Surgery	No improvment
Béjia I, Rtibi I, Touzi M, Zrour S, Younes M, Naceur B. Familial calcium pyrophosphate dihydratedepositiondisease. A Tunisiankindred. Joint Bone Spine 2004;71:401–8.[23]	2004	Family study	Five patients had pseudogout 1 lumbar spine	Diffuse CPPD			
Greca I, Ben Gabr J, Perl A, Bryant S, Zaccarini D. Trauma Induced Calcium Pyrophosphate Deposition Disease of the Lumbar Spine. Case Reports in Rheumatology 2020;2020:1–5.[16]	2019	Case report	80-year-old female with no known history of inflammatory arthritis left lower extremity weakness and fall progressive back pain.	CT scan MRI Image-guided biopsy and aspiration of the L4L5 vertebral bone	Advanced degenerative joint disease with severe spinal stenosis at the level of the lumbar 4-lumbar 5 (L4-L5) spinal segment vertebral Body edema and enhancement most evident at the L4L5 level and paravertebral soft tissue thickening seen at the L5-S1 level concerning of osteomyelitis/diskitis. calcium pyrophosphate crystaldeposition	0.6 mg daily. Steroids were stopped on day 7 as initial symptoms improved.	Missed her appointment
Yayama T, Baba H, Furusawa N, Kobayashi S, Uchida K, Kokubo Y, et al. Pathogenesis of calcium crystal deposition in the ligamentum flavum correlates with lumbar spinal canal stenosis n.d.:7.[5]	2005	Retrospective study	119 surgical cases with symptomatic lumbar spinal stenosis	Histological examination			

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Table 1 (Continued).

Reference	Year	Study Design	Clinical Features	Diagnostic Method	Outcomes	Treatment	Follow-Up
Ogawa Y, Nagatsuma M, Kubota G, Inoue G, Eguchi Y, Orita S, et al. Acute Lumbar Spinal Pseudogout Attack After Instrumented Surgery: Spine 2012;37:E1529–33.[30]	2012	Case report	72-year-old man presented with a 12-month history of bilateral sciatica Pain in his buttocks and the lateral aspects of his legs. severe lower back pain at 4 weeks after surgery but not fever.	Plain radiographs MRI MRI Biopsy Surgery	L4–L5 disc narrowing and L4 Spondylolisthesis severe spinal canal stenosis at L4–L5 on T1- andT2-weighted images changes in signal intensities of vertebrae and existence of fluid in the posterior back muscles on T1- and T2-weighted images Negative CPDD	Surgery: posterior lumbar transforaminal interbody fusion Conservative therapywithoutantibiotics	Symptom-free for 4 weeks Symptoms disappeared No destruction Improvment
Hakozaki M, Sekine T, Otani K, Konno S. Acute pseudogout lumbar discitis resembling acute pyelonephritis in an elderly woman. Intern Med J 2019;49:1048–50.[27]	2019	Letter to the editor	89-year-old woman presented with a 1-day history of acute low back pain	Laboratory parameters X ray CT scan and MRI Aspiration of the paravertebral cyst Radiography of the knee	White blood cell count 16,700/μL; serum uric acid 3.7 mg/dL and C-reactive protein (CRP) 204 mg/L Spondylotic/osteoporotic change with multiple compression fractures Presence of fluid in a paravertebral cyst on the left at L5/S disc space with circumscribed enhancement of the cystic wall CPDD Meniscal CPPD	Cefazolin sodium (3 g/day). NSAIDs	Improved: fever disappeared
Kleyer A, Knitza J, Schett G, Manger B. Calcium pyrophosphate deposition disease induced inflammatory back pain. Rheumatology 2019:kez225.[28]	2019	Letter to the editor	Woman, 82 year old acute onset of severe lumbar pain the patient developed acute arthritis in her right knee, right wrist and MCP 2 joint	MRI X ray CT scan	A spondylodiscitis in the lumbar spine CPPD Massive calcified deposits within vertebral discs, facet joints and spinal canal	IL-1 receptorantagonist, anakinra	Clinical signs disappeared and CRP normalized
Cacciotti G, Novegno F, Fiume D. Calcium pyrophosphate dihydrate deposition disease of the filum terminale. Eur Spine J 2013;22:501–5. https://doi.org/10.1007/s00586-013-2723-7.[17]	2013	Case report	50-year-old woman, affected by CPPDD diagnosis of chondrocalcinosis had been made at the age of 36 progressive weakness of both lower limbs associated with neurogenic claudication after 50 m of walking	CT MRI Histopathology	The presence of two intradural calcified lesions (8 and 11 mm in diameter, respectively) at level L3–L4, with no post-contrast enhancement Irregular massive deposits of prevalently rod-shaped calcium pyrophosphate dihydrate crystals of various size	L3–L4 laminectomz	Immediate symptoms relief. No recurrence
Pytel P, Wollmann RL, Fessler RG, Krausz TN, Montag AG. Degenerative Spine Disease: Pathologic Findings in 985 Surgical Specimens. Am J Clin Pathol2006;125:193–202.[6]	2006	Retrospective	Histologic features of 985 extradural spinal surgery specimens		Calcium pyrophosphate crystals was present in 2.8%, predominantly within diskmaterial.		

Abbreviations: MRI, magnetic resonance imaging; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; CRP, C Reactive Protein; CPPD, Calcium pyrophosphate dihydrate disease; CT, computed tomography; LBP, low back pain.

Characteristics of the Patients

The age ranged between 39 and 89 years old. Among patients with lumbar spine deposits of CPPD, 32 were women.[7–21] In the other studies, the epidemiological characteristics such as age and gender were not mentioned, as they concerned histological specimens of operated discs.[3–6] A history of CPPD was present in 40 patients.[17,20,22,23] Five patients had more than two comorbidities including diabetes, hypertension, coronary artery disease, hypothyroidism, gout, prostate cancer, stomach, and cervical tumor.[8,11,14,18,24,25]

Clinical Features

Duration of Symptoms and Background Circumstances

- The duration of symptoms varied between one day (acute back pain)[10,14,15,22,26–28] and 8 years.[9] The affection has been discovered during back pain in 22 cases.[7,11,12,15–19,21,29,30] Sciatica has been observed in 13 patients.[12,15–19,21,26,29,30] Neurological signs revealed the disease in 9 cases[15–19,26,29,31,32] and consisted in dorsiflexion weakness,[15–17,19,26] stiffness,[31] hypesthesia,[32] paresthesia,[15,33] foot drop and numbness[18] with residual urine sensation,[29] urinary retention,[15] and abnormal tendon reflexes.[15] Fever was present in 6 cases.[7,10,14,25,27,33] In two cases, the symptomatology led to a misdiagnosis of a urinary tract infection.[10,27]
- In 5 studies, the diagnosis was made on histological specimens of patients operated on for degenerative spine, canal stenosis, or disc disease.[3–6,20] Moshrif et al diagnosed 24.3% of lumbar CPPD among 152 patients with a history of peripheral CPPD (knees, wrists, shoulders, hip, and pubic symphysis).[20] Gruber et al found 14.69% lumbar CPPD among patients operated for herniated discs, degenerative disc disease, and recurrent disc herniation.[20] In the study conducted by Yayama et al, 62/206 (30.1%) of the discs taken from patients operated on for asymptomatic narrow lumbar spine, and 37/64 (57.8%) in patients operated on for spondylolisthesis showed deposits of calcium pyrophosphate.[5] Ariyawatakul et al led a retrospective study on lumbar spinal stenosis patients who had undergone a decompressive laminectomy. Histological examination identified eighteen patients among 34 that had CPPD.[4]

Diagnostic Method

Imaging

- Among the 62 patients, plain radiographs (X-ray) have been required in 13 cases,[8,10–14,17–20,24,26–28,30] and showed calcifications in 2 cases.[8,28] X-rays have mainly allowed diagnosing an underlying pathology such as degenerative spinal disease, spondylolisthesis, collapse fractures, or indirect signs of the narrow spinal canal.
- A CT scan has been prescribed in 15 cases,[9,11–13,15–18,20,22,25–29] and has detected calcium deposit in 7 of them (61%).[11–13,17,20,22,28] The lesions observed on CT scan were: calcium deposit in intervertebral joints,[13,22,28,29] calcified cystic lesion,[9,11] interspinous bursitis,[13] calcification of the ligamentum flavum and the intervertebral disc,[20] or degenerative joint disease.[16] The CT scan was useful for performing a CT-guided biopsy for the histological diagnosis of the lesion.[7,16,25] In two of the five cases where X-ray and CT scans were available, CT scan showed calcifications while plain radiographs were normal.[11,13]
- MRI: The elementary lesions observed in the MRI images were: increased signal within the intervertebral disk on the T1 and T2-weighted sequences,[26] an increased signal of the lumbar facet joints compatible with inflammation,[7,13,16,25,30] degenerative disc disease,[8,14,24] calcified or not cystic lesion at the side of the facet joints,[9,11,19,26,27] intramedullary mass mimicking a schwannoma,[12,24] extradural heterogeneous mass-like lesion in the anterior epidural space.[29] Spondylodiscitis/osteomyelitis was observed in 7 cases;[7,10,16,21,22,25,28] and was associated to an image of epidural phlegmon in one case,[26] Gadolinium-enhanced T1 hypersignal in two cases,[13,27] intradural calcified lesions with no post-contrast enhancement in one case.[17] The image of an abscess was found in 2 cases.[22,25] A cord compression was reported in 6 cases.[8,15,18,19,29,30] MRI showed calcifications or a chalky material in 4 cases.[9,11,17,18]

Histological Examination

Biopsy and Needle Aspiration. A disco vertebral biopsy was performed to eliminate spondylodiscitis based on the MRI features in 3 patients.[7,16,25] A percutaneous soft tissue biopsy was performed in 3 cases.[22,26,27] An aspiration of the

facet joint effusion and the cerebrospinal fluid for bacteriological examination in 2 cases.[14,15] Histological examination established the diagnosis of CPPD in 21 patients among all studies including the retrospective ones.[8,9,11–19,21,22,24,25,27–30]

Treatment

Medical Treatment

NSAIDs were prescribed in 5 cases[7,10,13,16,27] with clinical and biological improvement. Colchicine was used in 2 cases and the symptomatology disappeared under treatment.[16,22] Interleukin-1 receptor antagonist (Anakinra) was prescribed in one patient with clinical and biological improvement.[28] Antibiotics (Ceftriaxone) were attempted in one case even if no microorganism was found, and the patient improved significantly.[25] A low-dose steroid (Decadron) (6 mg every 6 hours, stopped at day 7) has been used in one case.[16]

Surgical Treatment

Surgery was attempted in 13 patients.[8,9,11,12,17–19,21,24,26,29,30] In all cases, surgery was performed for an etiology other than CPPD: either for decompression, tumor resection, or laminectomy. Histological examination was performed on surgery specimens in patients who underwent surgical interventions for different pathologies. CPPD was found after tumor resection of a schwannoma-like mass,[12,24] surgical decompression of a herniated disc[8] or a compressing mass[9,11,19,29] or radiographic bony destruction with sterile culture on biopsy,[26] neurological symptoms requiring a laminectomy,[17,18] spinal stenosis caused by a posterior bony protrusion from a collapsed vertebral body[18] or a worsening discitis despite well-conducted medical treatment.[21] Improvement after surgery was observed in 8 patients[8,11,12,17–19,26,29] and not mentioned in one patient.[24] A therapeutic failure was observed in two cases.[21,30] In one case, after the failure of surgical decompression, a second surgery was performed (distal L4 and proximal L5 laminotomies followed by flavectomy and medial facetectomy to expose the cyst.).[22]

Discussion

This review aimed to evaluate the involvement of the lumbar spine in CPPD. Most of the studies included were case reports (n = 20), suggesting that this pathological feature is still uncommon. However, through this review, we were able to show that the axial CPPD is not only rare, but also underdiagnosed, regarding the non-specificity of clinical signs, and the variable performance of imaging techniques.

In our review, spinal deposition of calcium pyrophosphate crystals was reported in 62 patients. The diagnosis of axial CPPD was made in the majority of cases postoperatively, on histopathological specimens in patients who initially consulted for chronic lower back pain. In those studies, the prevalence of spinal CPPD varied between 14.7% and 57.8%. Most of the patients were women, aged between 39 and 89.

A cross-sectional study involving 2157 cases of CPPD in US veterans reported a point prevalence of 5.2 per 1000, all joints included, with an average age of 68 years and 95% of male prevalence.[34] However, to our knowledge, the prevalence of lumbar spine CPPD has not been reported.

Among the case reports, most authors reported that a chronic symptom of CPPD in the lumbar spine which was lower back pain and radiculopathy due to compression of spinal nerves. CPPD of the lumbar spine was usually asymptomatic. Many of the patients with CPPD were elderly and have unrelated degenerative disease of the spine. However, CPPD can produce severe degenerative disk disease, often involving multiple levels.[35] The thoracic and lumbar regions are often affected, especially at the L2-L3 disc level.[36]

As the clinical features are not specific, imaging is required for diagnosis. The radiographic presentation of spinal CPPD can vary from simple calcium deposit to spinal masses, tophi, and hematomas causing compressive phenomena. Its diagnosis can be challenging because of this radiographical ambiguity and its relationship to osteoarthritis.[21] In this review, conventional radiographs showed disc calcifications in only 2 out of 13 patients. Studies have shown that arthropathy can precede radiographically detectable cartilage calcification, and the calcification may not always be dense enough to be visualized on conventional radiographs, or it may be difficult to identify if the joint is severely damaged.[37] In one study of 3228 patients undergoing knee arthroscopy, a radiographic diagnosis ofkneeCPPDwasmade in only 4% of patients with pathologically proved CPPD crystal deposition.[38]

A systematic literature review and meta-analysis supported the high specificity and low sensitivity of conventional radiography in the diagnosis of CPPD and showed that ultrasound was more sensitive and less specific than plain radiographs in detecting CPPD.[39]

When the conventional radiography is non-effective, a CT scan may help to detect calcifications. In this review, CT scan showed calcifications while plain radiographs were normal in only two cases, but this can be explained by the fact that X-ray was not performed or not mentioned in 13 cases. In the study led by Moshrif et al, CT scan was more sensitive than conventional radiography in detecting intervertebral disc and vertebral ligament calcification.[20]

MRI showed calcifications or a chalky material in 4 cases.[9,11,17,18] It has been reported that MRI was poorly sensitive to detect calcium deposits because CPP-containing tissues seem isointense to neural tissue on T1 weighted images and iso to hyperintense on T2 weighted sequences but were able to reveal endplate and disc inflammation.[20] Our review showed that MRI misled the diagnosis in several situations. Indeed, the hyper signal related to the edema and the juxta-articular collections related to calcified cysts were confused with an infection and epidural abscesses. For example, in the case described by Petit et al, MRI showed short-tau inversion recovery (STIR) hyper signal on the lumbar facet joints.[7] Grobost et al reported the appearance of L4-L5 spondylodiscitis, with epidural abscesses, Gadolinium-enhanced signal in L4-L5 zygapophysial joints, and intervertebral lumbar disks.[22] In the case reported by Mikhael et al, MRI showed an increased signal within the L5-S1 intervertebral disk and the endplates of the L5 and S1 vertebrae on the T1 and T2-weighted sequences.[26] Pazkad et al showed an increased signal consistent with inflammation.[25] In this study, CPPD was complicated by authentic osteomyelitis and the patient improved under antibiotics.[25] Another misleading image on MRI was compressive mass, which corresponds to a calcified cyst. MRI detected a cystic lesion at the side of the facet joints in 5 cases,[9,11,19,26,27] an intramedullary mass mimicking a schwannoma in 2 cases,[12,24] and an extradural heterogeneous mass-like lesion in the anterior epidural space in one case.[29]

It has been demonstrated that subchondral cysts are among the hallmarks of this arthropathy. The cysts usually are larger, more numerous, and more widespread than those in osteoarthritis. Cysts may form before cartilage loss is evident.[35] This proves the diagnostic difficulty in front of a compressive mass on MRI when calcifications are not visible. In this case, the CT scan may be an alternative before proceeding with the biopsy.

The discovertebral biopsy, despite its invasive character,allowed to make the diagnosis in almost 21 patients.[3,5–9,11,12,14,16–19,21,22,24–26,29,31] It often showed a fibrous tissue with positive birefringent crystal deposits.

CPPD crystals may be deposited in the ligamentum flavum and posterior longitudinal ligament, leading to myelopathy, cord compression, and spinal stenosis.[40,41]

In our review, surgery was attempted in all cases where there was a compressive mass, a degenerative spine with a surgery indication, or in the event of failure of medical treatment, and was always efficient.[8,9,11,12,17–19,29,31–33,42] It consisted of a decompressive surgery in the majority of cases. As for pharmacological treatment, it consisted of NSAIDs, Colchicine, and Interleukin-1 inhibitor (Anakinra). Studies that have looked at the treatment of axial CPPD have compared it to that of gout. As both crystal diseases are mediated by IL-1-driven processes, the therapeutic intervention first targets acute inflammation consisting of Colchicine, NSAIDs, and glucocorticoids.[43]

In a systematic review of the literature summarizing the management of CPPD, intravenous Colchicine demonstrated efficacy in pain and seizure reduction. Methotrexate was effective over an average duration of 7.4 weeks of treatment. Hydroxychloroquine was efficient in 85% of patients, with 50% responding within a month. Significant improvement in pain and objective assessment was observed with Magnesium Carbonate supplementation, with a pronounced placebo effect. Anakinra efficiency was also reported. ACTH analogues led to the resolution of pseudogout attacks within 4.2 days. Tocilizumab improved disease activity in all patients after 3 months-treatment but had some adverse effects.[43]

Clinical experience supports the effectiveness of NSAIDs in CPPDarthritis. However, to our knowledge, there are no clinical trials of NSAIDs in this condition. Despite this, they are recommended as one of the first-line treatments for acute CPP crystal arthritis.[44] NSAIDs should be prescribed with caution, given the risk of toxicity and since patients with CPPD are usually elderly with multiple comorbidities. Low-dose steroids have been used in one case.[16] This is particularly relevant in elderly individuals with comorbidities. No recent data has added to our knowledge of the use of Glucocorticoids in CPPD.[44]

The major advance in the management of CPP crystal arthritis over the last decade has been the use of biological agents. Martinon et al demonstrated that CPP crystals are capable of activating the inflammasome NLR-P3- caspase1-interleukin-1beta (IL-1b) pathway present in innate immune cells such as neutrophils.[45] Three IL-1b blocking agents are currently authorized for humans by the FDA: a monoclonal antibody against IL-1b (canakinumab); a recombinant IL-1 receptor antagonist (anakinra); and a dimeric fusion protein of IL-1 receptor and IL-1 receptor accessory protein (rilonacept).

Anakinra use was described in cervical and thoracic spine CPPD, in association with Colchicine is a 3-days course and the patient improved.[33] In peripheral arthritis, Anakinra showed efficiency in decreasing pain and was well-tolerated.[46–49]

In our review, it was used in only one study, with a clinical and biological improvement.[28]

Conclusion

CPPD of the lumbar spine is an underdiagnosed pathology due to its nonspecific clinical features and its radiographic ambiguity, often associated with degenerative changes.

Through this review, we tried to identify the most frequent clinical and imaging features, but also the misleading clinical signs and diagnostic pitfalls of this disease (Table 2). In case of inflammatory back pain in elderly subjects, without an infectious gateway, the diagnosis of CPPD should be systematically considered, especially if the patient has a history of spinal surgery or degenerative changes on standard radiography. The absence of calcifications on conventional radiographs does not rule out CPPD. The CT scan is more sensitive than conventional radiographs to visualize calcifications and should be requested in case of doubt.

When MRI is indicated, because of neurological or infectious signs, the diagnosis of CPPD is still appropriate, even if the images are in favor of spondylodiscitis or osteomyelitis, since it can masquerade calcifications. Lumbar spine CPPD can even mimic a compressive cystic mass. In these two cases, the discovertebral biopsy is the Gold Standard and should be performed whenever the diagnosis is uncertain. It shows, in most cases, deposits of birefringent crystals in polarized light. The treatment is not well-established and includes a medical and a surgical component. As for the pharmacological

Table 2 Summary of the Most Common and Misleading Clinical and Imaging Features in CPPD

Most Frequent Clinical and Imaging Features	Misleading Clinical Signs and Diagnostic Pitfalls
Clinical signs: Back pain Sciatica Neurological signs Fever	Clinical signs: - Urinary tract infection - Spondylodiscitis (fever + back pain+ compatible MRI signs) - Tumor (back pain+ cord compression+ mass)
Imaging: Plain radiographs (X-ray): - Calcifications - Degenerative spinal disease, spondylolisthesis, collapse fractures or indirect signs of narrow spinal canal.	Imaging: X-ray: degenerative signs can mislead the diagnosis into lumbar osteoarthritis
CT scan: Calcium deposit in intervertebral joints Calcified cystic lesion Calcification of the ligamentum flavum and the intervertebral disc Degenerative joint disease Help for the histological diagnosis of the lesion with CT-guided biopsy	CT scan: Interspinous bursitis
- MRI: - Increased signal within the intervertebral disk on the T1 and T2-weighted sequences - Increased signal of the lumbar facet joints - Degenerative disc disease - Calcified or not cystic lesion at the side of the facet joints - Intradural calcified lesions with no post-contrast enhancement - Calcifications or a chalky material	MRI: - Intramedullary mass mimicking a schwannoma - Extradural heterogeneous mass-like lesion in the anterior epidural space - Spondylodiscitis/osteomyelitis, sometimes associated with an image of epidural phlegmon - Gadolinium-enhanced T1 hypersignal – Image of an abcess - A cord compression

treatment, NSAIDs (to be used with caution), or low-dose glucocorticoids could be efficient. Interleukin 1 inhibitors are an innovative alternative given their mechanism of action. Finally, surgery is useful when CPPD is associated with degenerative phenomena, compressive cysts or if it is responsible for spine stenosis.

Disclosure

The authors report no conflict of interest in this work.

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