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Calcium pyrophosphate dihydrate deposition in degenerate lumbar discs

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Abstract Calcium pyrophosphate dihydrate (CPPD) crystal deposition in lumbar intervertebral discs has been described, but its clinical significance remains unclear. The present study analyzed histological sections of lumbar discs that were obtained from patients undergoing anterior lumbar interbody fusion. Immunohistological staining was undertaken to identify neural elements and blood vessels. Patients with CPPD deposition were compared with a group without CPPD deposition undergoing the same operation. CPPD was found in 15.7% of investigated patients (12.6% of analyzed discs). Deposits were found in areas of the annulus and nucleus showing advanced degeneration. Two patterns

were identified: one comprised sharply demarcated rounded deposits, while the other showed diffuse deposition of crystals. There was no association with ingrowth of vascular or neural tissue. Clinical data did not differ significantly in the two groups of patients. However, in all patients with CPPD deposition there was a history of trauma, previous surgery, or both. Isolated CPPD deposition in lumbar intervertebral discs appears to be an incidental finding that is not related to systemic diseases or general arthropathies.

Key words Lumbar disc · Degeneration · Histology · Calcium pyrophosphate dihydrate deposition

Introduction

The prevalence of calcium pyrophosphate dihydrate (CPPD) deposition in the skeletal system generally increases with age and becomes very common in the elderly [16]. Deposition of crystals may occur in the absence of clinical or radiographic features and is often observed as a purely incidental finding. However, patients may also present with an acute arthritis termed “pseudogout” [11] or chronic arthritic changes [3]. Typically the knee and wrist joints are involved [10, 15].

Involvement of the axial skeleton by CPPD is less common and occurs mainly in the lumbosacral and cervical spine, especially in the ligamentum flavum [9]. Deposits may reach considerable size and can mimic the symptoms of an acute herniated disc [6, 16]. CPPD deposits have

also been observed in lumbar disc fibrocartilage [4], but the clinical significance remains unclear.

The present study retrospectively analyzed histological sections of lumbar discs removed during anterior lumbar interbody fusion. Specimens with CPPD deposition were further investigated with specific immunohistochemical staining for nerve filaments and vascular endothelium. The group of patients presenting with CPPD in their disc specimens was also compared with a group of patients without evidence of crystal deposition.

Materials and methods

Histological material was available from 70 patients who underwent anterior lumbar interbody fusion for advanced degenerate disc disease involving 103 discs within a period of 2 years and 3

months. The disc material obtained at the time of surgery consisted of the anterolateral part of the annulus and part of the anterior nucleus. This block of tissue had been routinely embedded in paraffin wax and sectioned at 4 μ m for hematoxylin and eosin staining. The presence of CPPD deposits was determined by their characteristic rectangular or "rod and tablet" morphology and oblique extinction using crossed polarizer and analyzer on a light microscope [18]. If crystals were determined the patient was assigned to group A. Medical records of these patients were reviewed with particular reference to their histories, previous surgery, associated diseases, and laboratory tests. These data were compared with the findings in the group of patients (group B) with discs lacking CPPD crystals.

The histological sections of group A were further investigated by immunohistological staining for the neuronal protein gene product 9.5 (PGP 9.5; ultraclone, Wellow, UK) and for the vascular endothelial cell marker (QBend 10; Novocastra Laboratories, Newcastle-upon-Tyne, UK), using a standard avidin-biotin-peroxidase method with DAB = 3,3'-diaminobenzidine enhancement of the end product [8]. Antisera were used at dilutions of 1:20,000 (PGP 9.5) and 1:100 (QBend 10).

Results

Group A

CPPD deposits were identified in 13 discs of 11 patients, representing 15.7% of all patients in the study or 12.6% of all discs.

Three patients were female and eight were male. Average age at the time of operation was 49.4 years (range 36–71 years). Five patients had undergone a single-level fusion, and a two-level fusion had been performed in six (Table 1). In the latter, the CPPD crystals were found at one level only in four patients. All but one patient had undergone previous surgery at the same or an adjacent level,

and in five patients an intra-discal procedure had been performed, i.e., discectomy or chymopapain application. Nine patients could recall a specific incident, either an injury or a certain movement, as the onset of back pain. The history of low back pain ranged from 10 months to 27 years. Prior to the recent anterior fusion the maximal pain was graded between 5 and 8 on a 0–10 visual analog scale (VAS) by all patients. One patient suffered from diabetes mellitus, which has been reported to be commonly associated with CPPD [9]. Blood chemistry was available in two patients and showed no abnormalities of uric acid, calcium, or phosphate. Plain radiographs of the spine had been performed in all patients and MRI and/or CT investigation was available in nine patients. In no case had calcification of the disc spaces been reported.

Histological findings

CPPD deposits were found in the annular and nuclear regions of the disc (Table 2) and ranged from 0.2 to 62 μ m² in extent. Typically, deposits were observed in areas of the tissue that showed advanced degeneration with the presence of hypertrophic chondrocytes, cell clusters, and debris. Two patterns of deposits were identified:

1. Round or oval shape with a sharply defined margin, occurring either in discrete deposits or in clumps (Figs. 1, 2)
2. Irregular with no distinct margin (Fig. 3)

In one case, vascular ingrowth was detected beyond the normal range of the outer third of the annulus fibrosus,

Table 1 Clinical data of 11 patients with intradiscal calcium pyrophosphate dihydrate (CPPD) crystals

Patient/ date of op	Sex	Age at op	Levels fused	History	Previous treatment	Remarks
A. M./01.96	f	71	L4/5	1968 Back injury	1973 Postero-lateral fusion L5/S1	
B. A./12.96	m	54	L2/3	02.96 Lift + twist injury	Nil	
C. G./07.96	m	37	L4/5 L5/S1	1982 Back injury	1983 Chymopapain L4/5	Crystals L4/5 only
C. M./01.97	m	45	L4/5 L5/S1	1973 Back injury	1973 Laminectomy L3/4 1979 Laminectomy L4/5	Crystals both levels
H. D./04.96	m	44	L4/5 L5/S1	1987 Back injury	1992 Postero-lateral fusion L4/S1	Crystals L5/S1 only
P. C./06.96	m	36	L4/5 L5/S1	1989 Back injury	1989 + 93 Laminectomies L5/S1	Crystals L4/5 only
Q. F./10.95	m	39	L5/S1	1989 Twist injury	1989 + 93 Discectomies L5/S1	Histology without crystals, 1989
S. G./04.97	f	71	L3/4 L4/5	1974 No incident	1975 Laminectomy L4/5 1980 Laminectomy L5/S1	Crystals both levels
T. A./11.96	f	56	L4/5 L5/S1	1990 Back injury	1990 Dissect. + laminectomy L5/S1 1994 Re-exploration	Crystals L5/S1 only
W. P./03.96	m	43	L5/S1	1978 Back injury 1995 Back injury	1979 Dessect. + laminectomy L5/S1	
W. T./01.97	m	46	L5/S1	1985 No incident	1985 Discectomy L5/S1	

Table 2 Histological appearance of CPPD crystals in 11 patients (13 discs)

Name	Level	Location	No	Area of deposits (μm^2)	Margin
A. M.	L4/5	Outer annulus	1	19	Discrete
	L4/5	Nucleus	5	6–45	Ill-defined
B. A.	L2/3	Nucleus	2	10	Ill-defined
C. G.	L4/5	Inner annulus	9	1–6	1 Discrete 7 Ill-defined
	L4/5	Nucleus	2	4–62	Discrete
C. M.	L4/5	Mid annulus	4	2.5–18.3	3 Discrete 1 Ill-defined
	L5/S1	Annulus (all thirds)	5	1.6–25	3 Discrete 2 Ill-defined
	L5/S1	Inner annulus	1	6	Ill-defined
H. D.	L5/S1	Nucleus	9	1–7	Ill-defined
	L4/5	Inner annulus	4	6–38	2 Discrete 2 Ill-defined
P. C.	L4/5	Nucleus	25	0.5–37	Ill-defined
	L5/S1	Annulus (all thirds)	30	0.5–7	12 Discrete 18 Ill-defined
S. G.	L3/4	Inner annulus	22	0.4–5	13 Discrete 9 Ill-defined
	L4/5	Annulus (all thirds)	> 45	0.7–50	11 Discrete > 34 Ill-defined
	L4/5	Nucleus	> 10	0.5–50	1 Discrete > 10 Ill-defined
T. A.	L5/S1	Annulus (all thirds)	31	0.2–30	11 Discrete 20 Ill-defined
	L5/S1	Nucleus	8	20–30	Ill-defined
W. P.	L5/S1	Annulus (all thirds)	6	2–14	5 Discrete 1 Ill-defined
		Nucleus	15	3–6	Ill-defined
W. T.	L5/S1	Mid and inner annulus	24	2.1–25	9 Discrete 15 Ill-defined

Fig.1 Low-power view of calcium pyrophosphate dihydrate (CPPD) crystal aggregate in the inner annulus, with the largest group measuring $11 \mu\text{m}^2$ ($\times 40$ magnification) **Fig.2** Polarized-light view of a discrete CPPD crystal aggregate in the annulus measuring $30 \mu\text{m}^2$ ($\times 100$ magnification)

but there was no specific relation to the CPPD crystals. Otherwise, there was no evidence of vascular or neural ingrowth.

Group B

Thirty-two female and 27 male patients did not show CPPD deposits. Average age at the time of operation was

Fig. 3 Ill-defined crystal aggregate measuring $42 \mu\text{m}^2$ ($\times 40$ magnification)

42.6 years (range 26–69 years). This was not statistically different from group A, but there was a strong trend ($P = 0.057$ in a two-tailed Student's *t*-test).

Eighty-six discs (L2/3 $\times$ 1; L3/4 $\times$ 7; L4/5 $\times$ 35; L5/S1 $\times$ 43) were operated on in 34 single-level, 23 two-level, and 2 three-level fusions. In 35 patients (50 discs) no previous surgery or intradiscal therapy had been performed at the same or an adjacent level. Twenty-seven patients could not recall a specific injury or movement as their onset of back pain. The length of history varied between 6 months and 12 years, with an average of about 4 years. Prior to the reference anterior fusion the maximal pain was graded between 5 and 9 on a 0–10 VAS by all patients.

Discussion

The overall prevalence of CPPD deposits in lumbosacral discs of material gained at autopsy or surgery has been reported to be between 6% and 20% [5, 14] and 10% and 26%, respectively [1, 7, 9]. Most reports assume an association between disc degeneration and CPPD deposition due to changes in collagen and proteoglycan composition and concentration [5]. However, the specific interaction between degenerative processes and crystalline deposits is unclear. It has been hypothesized that CPPD crystals can accelerate the process of disc degeneration [17], while some authors have proposed previous surgery or trauma as a possible cause for CPPD deposition. Andres and Trainor [1] and Ellman et al. [4] reported CPPD crystals in 11 patients undergoing surgery for spinal cord or nerve root compression, and all of their patients had undergone prior surgery at the same or an adjacent disc space. In our study, patients presenting with intradiscal CPPD depositions tended to be older than comparable patients without. Ten of our 11 patients had a history of previous surgical inter-

vention. The importance of previous surgery may be illustrated by one case, in which the specimen obtained from a partial discectomy performed 7 years prior to the reference anterior fusion had not shown CPPD crystals. Furthermore, 9 of the 11 patients (82%) with intradiscal CPPD recalled a specific incident or trauma initiating their back pain history, whereas this was the case for only 54% of patients lacking CPPD.

We could not detect differences in the clinical presentation of the two groups, with the indication for surgery being severe discogenic low back pain in all patients. The length of history was variable in both groups. Markiewicz et al. [9] investigated tissues obtained from decompressive laminectomies and found a shorter and more intense disease course in their CPPD group compared to the non-CPPD group. While this would suggest an additional role of the crystals in causing pain, we did not find nerve tissue in association with intradiscal CPPD crystals. In patients with degenerative disc disease, the ingrowth of blood vessels and nerve fibers in the endplate region has been shown [2], but our histological sections did not contain endplate material to enable us to make an assessment of such features.

Intradiscal CPPD deposition does not appear to be associated with signs of generalized CPPD disease. Apart from one patient who presented with a long-standing history of knee pain and eventually underwent knee replacement, none of our patients had a history of general joint disorders or of pyrophosphate arthropathy (pseudogout), nor was there evidence of risk factors such as Chilean ancestry, hemochromatosis, hyperparathyroidism, true gout, or Wilson's disease [3, 12]. Our patients were also younger than the typical patient population for pseudogout [10, 13]. A higher prevalence of CPPD disease in women has been reported [3, 13] but this was not the case in our study (male to female ratio 3:1). The fact that in four patients with a two-level fusion CPPD was only found at one level also indicates a non-systemic condition in our patient group. As routine biochemical screening is generally regarded as unrewarding [3, 9], we did not investigate the patients for this purpose.

Conclusion

Patients with a history of trauma and/or previous spinal surgery seem more likely to present with localized CPPD deposition in lumbar intervertebral discs. As associated ingrowth of vascular or neurogenic tissue is lacking, a specific role for CPPD crystals in causing pain remains unproven. Therefore, localized intradiscal lumbar CPPD deposits appear to be an incidental finding unrelated to systemic disease or general arthropathies.

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