Calcium pyrophosphate dihydrate crystal deposition disease in the cervical ligamentum flavum

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The authors describe three cases of cervical radiculomyelopathy caused by calcium pyrophosphate dihydrate crystal deposition disease (CPPDdcd). Radiological investigations revealed nodular calcifications, 5 to 7 mm in diameter, in the cervical ligamentum flavum compressing the spinal cord. Light microscopic, scanning electron microscopic, and x-ray diffraction studies were performed on all three surgical specimens obtained by laminectomy. In two of the cases x-ray microanalysis and transmission electron microscope studies were also performed.

This study defined the presence of two patterns of crystal deposition in the ligamentum flavum. One is a nodular deposit, in which hydroxyapatite crystals are seen in the central part of the nodules, with calcium pyrophosphate dihydrate (CPPD) being distributed thinly around them. The other pattern is a linear deposit seen in multiple ligaments and composed of pure CPPD, which causes minimal thickening of the ligaments. A transitional pattern between the two types was also observed. This study revealed details of the nodular deposition of crystals in the ligamentum flavum and demonstrates that CPPDdcd and so-called "calcification of the ligamentum flavum" are the same disease: namely, CPPDdcd. Hydroxyapatite is assumed to have been transformed from CPPD.

KEY WORDS - spinal cord • ligamentum flavum • calcification • calcium pyrophosphate dihydrate crystal deposition disease • chondrocalcinosis

Calcium pyrophosphate dihydrate crystal deposition disease (CPPDdcd), also known as chondrocalcinosis, is a relatively newly described disease entity that occurs mainly in articular cartilage. Extra-articular CPPDdcd in the bursa, tendon, dura mater, and ligament has been reported less frequently. Although the pathogenesis of CPPDdcd has not yet been identified, the disease is known to occur frequently in the elderly and has a tendency to increase in severity with aging.

Recently, there have been reports of radiopaque calcified nodules in the cervical ligamentum flavum as a cause of cervical radiculomyelopathy. To date, about 30 cases have appeared in the literature, nine of which were proved to be CPPDdcd. The pathology in the other 21 cases was attributed to so-called "calcification of the ligamentum flavum." Deposits of hydroxyapatite were demonstrated in seven of these 21 patients, but no crystallographic investigation was undertaken on the deposits in the other 14 patients.

The presence of many similar clinicopathological features, such as the patients' age at onset, location of the deposit, and x-ray and histological findings, in both CPPDdcd and "calcification of the ligamentum flavum" seems to imply that these two conditions are closely related pathologically. However, the question of how the two different calcium-containing crystals develop in the two conditions has remained unsolved. This present report is a detailed pathological evaluation of sporadic (idiopathic) CPPDdcd in the cervical ligamentum flavum, which shows that the two above-mentioned diseases are the same disease entity: namely, CPPDdcd.

Clinical Material and Methods

Three patients with cervical radiculomyelopathy form the basis of this study. The patient in Case 1 was
a 63-year-old woman who started to feel a tingling sensation in her fingers 11 months prior to admission. The tingling was followed by clumsiness of the fingers and gait disturbance 4 months after the initial symptoms were noted. On admission, neurological examination revealed a spastic gait, muscle weakness in both hands, and exaggerated deep-tendon reflexes except for biceps reflexes which were hypoactive. The second patient (Case 2) was a 64-year-old woman who developed paresthesia in both hands and gait disturbance 6 months prior to admission. Neurological examination showed generalized hyperreflexia and localized hypesthesia in the C-7 region. The third patient (Case 3) was a 74-year-old man who developed paresthesia in the fingertips of both hands and gait disturbance, which gradually worsened during the 4-year period after the initial symptoms appeared. Neurologically, he was tetraparetic with generalized hyperreflexia and a positive Babinski sign bilaterally. Pain sensation was disturbed below the T-3 level and in both forearms.

In all three cases no abnormalities were noted in general physical appearance, blood, or urine. None of them exhibited diabetes mellitus, hemochromatosis, hyperparathyroidism, or gout. No abnormalities were detected on x-ray examination of the whole body, except for some linear calcification in the meniscus of the knee joint in Case 1.

Cervical x-ray films of the three cases are shown in Fig. 1. Faint radiopaque shadows were observed mainly at C4-5 in Case 1, a faint radiopaque shadow at C3-4 and a dense nodular calcification at C5-6 were demonstrated by tomography in Case 2, and a nodular calcification was noted at C4-5 in Case 3. All of the calcifications were present in the posterior part of the spinal canal, anterior to the interlaminar space.

In all cases the maximum spinal cord compression shown by myelography was at the site of the nodular calcification. En bloc C2–7 laminectomy improved the patients’ neurological symptoms significantly.

Specimens of the spinal lamina and ligamentum flavum obtained by laminectomy were examined by the following five pathological studies: 1) light microscopy with hematoxylin and eosin, some special stains, and polarized light; 2) scanning electron microscopy (SEM); 3) transmission electron microscopy (TEM); 4) energy-dispersive x-ray microanalysis with SEM and TEM; and 5) x-ray diffraction study of the crystals. Pathological Studies 1, 2, and 5 were performed in Case 1, and all of the studies were performed in Cases 2 and 3. Studies 2 to 5 were made on undecalcified specimens.

Results

The results of the studies in the three cases were almost identical. These studies revealed patterns of crystal deposition in the ligamentum flavum that could be roughly divided into two types: a nodular deposit and a linear deposit. Another type, considered to be transitional between these two types, was also noted.

Nodular Deposition

Macroscopically, the nodules were elongated and globular, 5 to 7 mm in diameter, and located within the ligamentum flavum. Their surface was covered with thin ligamentum flavum tissues. Upon cutting the nodules, a chalky white substance was observed inside and

![Fig. 1. X-ray films of the cervical spine in Cases 1 to 3. Left: In Case 1, nodular calcification is revealed at C4–5 (arrows). Center: In Case 2, there is faint calcification at C3–4 (arrows, upper), and tomography demonstrated dense nodular calcification at C5–6 (lower). Right: In Case 3, tomography showed nodular calcification at C4–5 (arrows).](image-url)
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a rough granular substance with a paste-like consistency was present in the central part of the deposition.

Light microscopic examination revealed two types of deposit in the nodules, one surrounding the other (Fig. 2). The outer deposit was an amorphous or finely granular substance, which showed positive with von Kossa's stain and which had positive birefringence under polarized light. The layer was 10 to 100 μ thick, and when a part of the layer was absent the internal deposit was directly adjacent to the surrounding ligamentum flavum tissue. The inner part consisted of deposits of various shapes, some of which were round or angulated. In the ligamentum flavum around the nodules, sporadic chondrocytes and large quantities of foreign-body granulation tissue were occasionally seen. There was no continuity between the nodules and the spinal laminae. The specimens from the outer layer and inner part of each nodule were prepared separately for SEM, TEM, and x-ray diffraction evaluation as follows.

Scanning electron microscopy revealed that the amorphous, finely granular substance in the outer layer of the nodules consisted of plate-shaped crystals 0.5 to 1.5 μ long (Fig. 3). In contrast, "microspheroids" were seen filling the central part of the nodules (Fig. 4). These microspheroids had a variety of shapes, from perfect spheroids to distorted ones, and were 0.1 to 30 μ in diameter. Plate-shaped crystals were rarely found in the central part of the nodules. Individual analysis of each crystal with x-ray microanalysis indicated that the Ca:P ratio was 1 in the plate-shaped crystals and Ca:P = 1.5 to 1.8 in the microspheroids. The former showed a similar basic composition to calcium pyrophosphate dihydrate (CPPD), the latter to hydroxyapatite.

Transmission electron microscopic observation of the ligamentum flavum around the nodules showed that many plate-shaped crystals were distributed between the elastic fibers and that some of them were phagocytosed by macrophages. An increase in the number of collagen fibers and a degeneration of elastic fibers were observed at sites far from the margin of the nodules. Many matrix vesicles with various electron densities were present in the extracellular space distributed around the degenerated elastic fibers (Fig. 5). By x-ray microanalysis, the vesicles were shown to be 60 to 360 nm in diameter and were composed of different ratios of Ca, P, Cl, and sometimes Si. Occasionally, a Ca + P complex was also recognized within the degenerated elastic fibers.

X-ray diffraction studies confirmed that the ingredi-
ent of the plate-shaped crystal was CPPD and that of the microspheroids was hydroxyapatite (Fig. 6).

**Linear Deposition**

Macroscopic findings of the linear deposition at the C3–4 level in Case 2 are shown in Fig. 7 left. Linear deposition, which was observed in the cut surface of the ligamentum flavum, was actually a coalescence of small foci of deposits which were distributed in the middle layer of the ligamentum flavum. With light microscopy the deposit appeared to consist of a pure amorphous, finely granular substance (Fig. 7 right). With polarized light the deposit showed birefringence, it appeared by SEM to be made up of a plate-shaped crystal, and it had a Ca:P ratio of 1 with x-ray microanalysis. The x-ray diffraction pattern of the deposit coincided with that of CPPD.

This type of deposit was present to a greater or lesser degree in all ligamenta flava studied. The ligamentum flavum tissue surrounding the deposit frequently showed a marked granulation-tissue response accompanied by multinucleated giant cells. Mucoid degeneration, loosening of elastic fibers, and an increase of collagen fibers were frequently noted in the ligamentum flavum tissue adjacent to the deposit. Sporadic chondrocytes were also present. In most specimens the linear type of deposit caused minimal thickening of the ligamentum flavum. A schematic drawing of the distribution of the crystals in the nodular and linear types of deposition is shown in Fig. 8.

**Transitional Pattern**

In Case 2, the crystal deposition pattern on the opposite side of the ligamentum flavum, which contained nodules at the C5–6 level, was particularly interesting. This nodular deposition had a diameter of 3 to 4 mm, and caused a moderate thickening of the ligamentum flavum. The deposited crystal consisted of CPPD alone. This deposit was considered to represent a transitional pattern between the nodular and linear types.

**Discussion**

It has been assumed that CPPD is in the ligamentum flavum and ossification of the ligamentum flavum are completely different diseases. The former is characterized by crystal deposition which is mostly localized in the cervical region and has no continuity with the spinal lamina; the latter is characterized by ossification which occurs most frequently in the thoracic and lumbar regions and has continuity with the spinal lamina.26,42

Kawano, et al.,37 recently reported a case in which a nodular deposition in the ligamentum flavum consisted of CPPD and hydroxyapatite, with hydroxyapatite located in the central part of the nodules and CPPD being...
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**FIG. 6.** X-ray diffraction patterns of the crystals. Filter: Ni; voltage: 40 kV; current: 45 mA; collimator: 100 µm. The numbers show the diffraction value of each peak. **Left:** An x-ray diffraction pattern of the plate-shaped crystals (upper) and the standard pattern of calcium pyrophosphate dihydrate (CPPD) (lower) are shown. The two patterns coincide well. **Right:** An x-ray diffraction pattern of microspheroids (upper) and the standard pattern of hydroxyapatite (lower) are shown. The two patterns coincide well.

**Fig. 7.** **Left:** Horizontal cross section of the ligamentum flavum at the C3-4 level in Case 2 showing linear deposits distributed in the middle layer of the ligamentum flavum. Undecalcified specimen. **Right:** Light micrograph of the specimen seen at left showing small foci of deposits. With polarized light, positive birefringent crystals are seen in the deposition, accompanied by foreign-body granulation tissue. With scanning electron microscopy, energy-dispersive x-ray microanalysis, and x-ray diffraction the crystal was confirmed to be calcium pyrophosphate dihydrate. Undecalcified specimen: H & E, × 90.

distributed thinly around it. The present study further confirmed these findings. This new information is of pathological importance because only hydroxyapatite would have been detected if only the central part of the nodules had been examined. Analysis of the crystals in different parts of the nodules has not been made in past studies of so-called “calcification of the ligamentum flavum,” in which only the existence of hydroxyapatite has been demonstrated. It must be stressed that CPPD will be detected if the components in the margin of the nodules are examined.

A comparison of CPPDcdd with “calcification of the ligamentum flavum” is shown in Table 1. There are many features common to the two diseases, such as the patients’ age at onset, the site of nodular calcification, and the x-ray and histological findings, but the type of deposited crystals is different. These clinicopathological similarities and the results of our study have led to the conclusion that these two diseases are the same.

Concerning the relationship between CPPD and hydroxyapatite in nodular calcifications in the ligamentum flavum, the deposition of CPPD is suspected to
FIG. 8. Schematic drawing showing the distribution of calcium pyrophosphate dihydrate (CPPD) and hydroxyapatite in the ligamentum flavum. Hydroxyapatite is seen in the most central part of the "nodular deposition," with CPPD being distributed thinly around it. The "linear deposition" consists of CPPD alone.

FIG. 9. Probable growth pattern of the crystal depositions. At the initial stage (upper sketch), calcium pyrophosphate dihydrate (CPPD) crystal depositions collect in a linear fashion in the ligamentum flavum. In the next stage (center sketch), the amount of CPPD crystals has increased. In the last stage (lower sketch), the deposition grows larger and the central part of CPPD is transformed into hydroxyapatite.

occur first, followed by a transformation of CPPD to hydroxyapatite in the central part of the nodules (Fig. 9). The evidence for this is as follows. 1) Linear depositions consisting of CPPD alone have been found in many ligamenta flava, but no depositions consisting of hydroxyapatite are reported. 2) Small nodular deposits containing CPPD alone have been found. These are considered to be a transitional pattern between the nodular and linear types of deposition. 3) In the process of physiological calcification or ossification, it is generally accepted that combining calcium ions and phosphate in tissue produces calcium pyrophosphate, brushite, or octacalcium phosphate, and finally hydroxyapatite. 4) The transformation of hydroxyapatite to other calcium-phosphate complexes is difficult, as hydroxyapatite is extremely stable chemically. 5) It has been demonstrated that, once CPPD has been transformed into hydroxyapatite in vitro, the surface of the hydroxyapatite acts as a catalyst and accelerates the transformation of CPPD to hydroxyapatite.

According to the five considerations, it may well be assumed that the basic mechanism of the nodular deposition in question is CPPDcdd. The biochemical conditions under which CPPD is transformed into hydroxyapatite are still unknown.

**TABLE 1**

<table>
<thead>
<tr>
<th>Factor</th>
<th>CPPDcdd</th>
<th>Calcification of LF</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>patients’ age (yrs)</td>
<td>61–80 (median 68)</td>
<td>52–72 (median 65)</td>
</tr>
<tr>
<td>men:women</td>
<td>3:3</td>
<td>2:13</td>
</tr>
<tr>
<td>x-ray findings</td>
<td>nodular calcifications</td>
<td>nodular calcifications</td>
</tr>
<tr>
<td>location of calcification</td>
<td>cervical</td>
<td>cervical</td>
</tr>
<tr>
<td>joint abnormality</td>
<td>3 of 4 cases (knee)</td>
<td>not described</td>
</tr>
<tr>
<td>histology</td>
<td>amorphous–fine granular</td>
<td>amorphous–fine granular</td>
</tr>
<tr>
<td>identified crystal type</td>
<td>CPPD &amp; occasional hydroxyapatite</td>
<td>hydroxyapatite (7 of 21 cases)</td>
</tr>
</tbody>
</table>

* Comparisons were made between cases in the literature of calcium pyrophosphate dihydrate crystal deposition disease (CPPDcdd) and of so-called "calcification of the ligamentum flavum (LF)." The nine cases of CPPDcdd include the three cases described in the present report.

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We consider the characteristic deposition pattern of CPPDdcd in tissue to be as follows. Small foci of deposits coalesce to form linear deposits. This pattern was observed in this study, but the thickening of the ligamentum flavum resulting from linear deposits was too slight to cause compression of the spinal cord. This fact agrees with the results of the studies of Bywaters, et al., and Resnick and Pineda, and it is now clear that "innocent" deposition in the ligamentum flavum is commonly present in CPPDdcd.

The most important fact about CPPDdcd in the ligamentum flavum is that the depositions of CPPD form masses and compress the spinal cord. Descriptions in the literature of nodular deposits or tophus formation of CPPDdcd are rare, but the disease has been reported sporadically in the subcutaneous region of the finger, the subcutaneous region of the toe, the metacarpophalangeal joints, the temporomandibular joints, and the subcutaneous region of the elbow. The mechanism for development of these nodular depositions has not been explained in these cases. Ling, et al., assumed participation of local factors, and Leisen, et al., stated that "prolonged bathing of the periarticular tissues could then have resulted in a continuous deposition and tophus formation." Gerster, et al., reported an interesting case in which both CPPD and hydroxyapatite were found in the tophus in the subcutaneous region of the olecranon. However, they did not evaluate distribution of the two crystals in their case and did not discuss a causal relationship between them. The nodules in the present study contained CPPD and hydroxyapatite, the former deposit surrounding the latter. It seems reasonable to assume that hydroxyapatite simply represents the final phase of a common pathway of calcification in a large deposit focus. Whether or not the formation of hydroxyapatite plays a positive role in the nodule formation is still uncertain.

Regarding why CPPD is deposited preferentially in the ligamentum flavum, the degenerated products of elastic fibers may be related to this CPPD crystal deposition, since in our TEM study many calcium-containing matrix vesicles were identified around the degenerated elastic fibers. This agrees with the reports made by Yu and Blumenthal and by Kim which state that the elastic fibers play a major role in the initial phase of calcification. The preference of CPPD deposition for the cervical region may relate to the fact that the cervical region is more mobile than any other part of the spine and the cervical ligamentum flavum has more chance to receive minor injuries. As a result, greater degeneration of the ligamentum flavum combined with the aging process may cause the production of the milieu (the abnormal matrix) in which CPPDdcd easily occurs.

Most cases of CPPDdcd in the cervical ligamentum flavum and so-called "calcification of the ligamentum flavum" have been reported in Japan (29 of 30 cases). This is interesting, as it seems to coincide with the fact that ossification of the posterior longitudinal ligament occurs with a high frequency in Japan and East Asia. It is not obvious, however, whether the incidence of CPPDdcd in the ligamentum flavum is highest in Japan or whether the disease is overlooked in other countries.

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