Pathophysiology of Calcification and Ossification of the Ligamentum Flavum in the Cervical Spine

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KEYWORDS

• Calcification • Ossification • Ligamentum flavum • Cervical spine • Myelopathy
• Calcium pyrophosphate dehydrate

KEY POINTS

- Symptomatic calcification of the ligamentum flavum and ossification of the ligamentum flavum in the cervical spine are relatively rare compared with other degenerative cervical diseases.
- These diseases are associated with degenerative hypertrophy and a metaplastic mechanism of the ligamentum flavum related to the aging process; but mechanical, metabolic, and genetic factors are also involved.
- Clinical features are nonspecific compared with other degenerative cervical diseases; however, radiological and histopathologic studies can provide a precise diagnosis.
- Surgical decompression with adequate timing is required in most patients who present with relevant or progressive radiculomyelopathy.

INTRODUCTION

Degenerative change of the ligamentum flavum is a common finding associated with the intervertebral aging process. The main categories of ligamentous degeneration are hypertrophy, calcification, and ossification.[1] Symptomatic calcification of the ligamentum flavum (CLF) and ossification of the ligamentum flavum (OLF) in the cervical spine are relatively rare compared with other degenerative cervical diseases, although the performance of clinical and histopathologic investigations is increasing. This article summarizes the epidemiology, clinical appearances, radiological characteristics, and histopathologic findings of CLF and OLF in the cervical spine.

Calcification of the Ligamentum Flavum

Epidemiology and pathogenesis

CLF is a crystal deposition disease that mainly affects the central portion of the ligamentum flavum. Many previous articles have differentiated calcium pyrophosphate dihydrate (CPPD) crystal deposition disease from CLF. However, many patients develop compressive radiculomyelopathy without the painful arthropathy typically seen in CPPD deposition disease, also known

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as articular chondrocalcinosis or pseudogout.[2] Crystallographic analysis of patients with CLF frequently demonstrates not only CPPD but also other mineralized deposits, such as hydroxyapatite, calcium orthophosphate, and combinations of these.[3–5] Therefore, discrimination among these disorders is still difficult in many cases. The pathogenesis of CLF has been described in relation to the degenerated and thickened ligaments. Calcium deposits mainly occur in the central part of the ligamentum flavum, which is surrounded by degenerated elastic fibers. CLF ordinarily has no continuity with the lamina, and the superficial and deep layers of the ligamentum flavum are preserved.[1,6] Various factors reportedly play relevant roles in the development of CLF, including the aging process, endocrine imbalance, mechanical stress of the cervical spine, metabolic diseases, and chondrocytic metaplasia.[7,8] According to their histologic investigation, Kawano and colleagues[9] speculated that CPPD was first deposited in the ligamentum flavum and then transformation from CPPD to the stable final form of the hydroxyapatite crystal was induced particularly in the central area of the calcification.

Although the prevalence of CLF in the general population is unclear, Watanabe and colleagues[10] found that radiographic evaluation revealed positive findings of CLF in the cervical spine in only 15 of 1619 (0.9%) patients who complained of neck problems. Symptomatic CLF in the cervical spine was first reported by Nanko and colleagues[11] in 1976. The investigators described a 70-year-old woman with radiculomyelopathy at the C5-6 and C6-7 levels. Baba and colleagues[12] experienced 8 cases and reviewed 91 reported cases involving patients who underwent surgical treatment of cervical myeloradiculopathy caused by CLF. The investigators found that 85% of all patients were female and had an average age of 64.8 years (range, 39–80 years). Additionally, 81% of the lesions were between the C4-5 and C6-7 levels.[12] Previous reports have identified the following characteristics of patients with symptomatic CLF: most patients are female; most are aged greater than 60 years; the lower cervical spine is frequently affected; 1- or 2-level lesions are common; it is mostly reported in Asian populations; it is sometimes associated with cervical disc disease; acute neck pain accompanied by crystal-induced arthritis is uncommon; and concomitant calcium deposits are often observed in other articular or periarticular sites (commonly the knee joint, intervertebral disc, hip joint, pubic symphysis, and shoulder).[3,5,13,14] Almost all clinical reports of CLF describe involvement in the cervical spine; it is extremely rare in the thoracic spine.[15–17] Several cases of symptomatic CLF in the cervical spine have been reported from non-Asian countries.[18–21]

Clinical features and radiographic appearance

There are no characteristic neurologic symptoms or signs that distinguish CLF from cervical spondylosis and ossification of the posterior longitudinal ligament (OPLL). According to data compiled by clinical reviews, the most common initial symptom is a sensory disturbance, such as numbness, dysesthesia, or pain, with an incidence of greater than 80%.[22] A common symptom in patients on hospital visits is gait disturbance coexisting with an abnormal deep tendon reflex or objective sensory disturbance. Hand clumsiness is also frequently observed.[12,22] Mwaka and colleagues[23] described 26 patients with clinical, radiological, and histologic evidence of cervical cord compression by CPPD crystal deposition among 465 Japanese patients who underwent posterior decompression surgery. All patients complained of numbness in the upper and lower extremities except 4 who did not have numbness in the lower extremities. Gait disturbance, bladder dysfunction, and a radicular sign in the arm were observed in 85%, 42%, and 38% of patients, respectively. Abnormal reflexes were also apparent in 85%.

Many affected patients do not present with abnormal laboratory data related to inflammatory, calcium metabolism, and hormonal imbalances.[12] However, Imai and Hukuda[24] reported that the preoperative erythrocyte sedimentation rate and serum C-reactive protein concentration were abnormally high in 4 of 8 patients and the white blood cell count was transiently but abnormally high in one. After surgery, these data were normalized in all patients except one. Histologic analysis of the resected specimens showed that the 4 patients with a high preoperative erythrocyte sedimentation rate and C-reactive protein concentration had inflammatory granulation tissue adjacent to the ligamentum flavum. Although the calcification itself does not usually induce acute neck pain, Kobayashi and colleagues[25] reported an atypical case of severe acute neck pain caused by CLF in the cervical spine with an inflammatory blood examination. In that case, conservative treatment was not effective and surgical removal of the CLF provided complete resolution of the patient's symptom. The investigators speculated that a relationship was present between CPPD crystal deposition in the ligamentum flavum, which was histologically proven, and acute neck pain similar to a pseudogout attack.