The Cervical Spine in Calcium Pyrophosphate Dihydrate Deposition Disease. A Prevalent Case-Control Study

AXEL FINCKH, DANIEL VAN LINTHOUDT, BERTRAND DUVOISIN, PHILIPPE BOVAY, and JEAN-CHARLES GERSTER

ABSTRACT. ***Objective.*** To test the hypothesis that calcium pyrophosphate dihydrate (CPPD) deposition disease is a risk factor for neck pain.

Methods. A prevalent case-control study was conducted to assess cervical calcifications and neck pain between patients with and without known peripheral CPPD deposition disease. CPPD cases were included if diagnosed with CPPD deposition disease of peripheral joints, and excluded if their chief complaint was neck pain. Controls were randomly selected among consecutive patients, hospitalized for conditions unrelated to CPPD deposition disease or neck pain, and matched to CPPD cases by age and sex. Cervical calcifications were assessed by lateral cervical radiographs and computed tomography scans of the upper cervical spine; neck pain and cervical function were appraised by a validated questionnaire.

Results. Cervical calcifications were found in 24 out of 35 patients (69%) in the CPPD group compared to 4 out of 35 patients (11%) in the control group ($p < 0.001$). Patients with CPPD deposition disease reported significantly more neck pain and discomfort than controls ($p < 0.001$), and were 5 times more likely to report any neck pain (odds ratio 5.5; 95% confidence interval: 1.9, 21.9). Among male patients, more extensive cervical calcified deposits correlated with more severe neck pain ($r_s = 0.58$, $p = 0.03$).

Conclusion. These results suggest that CPPD deposition disease frequently involves the cervical spine and may be associated with the development of neck pain. (J Rheumatol 2004;31:545–9)

Key Indexing Terms:
CALCIUM PYROPHOSPHATE DIHYDRATE NECK PAIN CERVICAL SPINE CHONDROCALCINOSIS

Calcium pyrophosphate dihydrate (CPPD) deposition disease is a common rheumatologic disorder, especially among elderly patients. Rare under the age of 50, it ranges from 10 to 15% for ages 65 to 80, and over 20% for ages above 80[1]. Most often, CPPD crystals are quiescent and constitute merely an incidental finding on joint radiographs. Occasionally these deposits may become symptomatic and are expressed in different clinical patterns: as widespread osteoarthritis (OA), sometimes referred to as chronic pyrophosphate arthropathy; as a form of polyarthritis mimicking rheumatoid arthritis; or as an acute mono or oligoarthritis, often called CPPD gout.

CPPD deposition disease tends to be considered a disorder of the peripheral joints; however, involvement of the spine is not uncommon[2,3]. In the cervical spine, calcified deposits have been reported in almost every anatomical structure including the transverse ligament of the atlas (TLA)[2,4]. In these locations, CPPD crystals can trigger various conditions causing neck pain[5]. Inflammation secondary to CPPD crystals in the periodontoid region can produce acute episodes of neck pain, with cervical stiffness and fever, mimicking meningitis[6]. CPPD deposition disease has also been related to a severe form of cervical OA. Resnick, *et al*[7] found extensive abnormalities in the cervical spine in 91% of patients with CPPD disease, ranging from disc space loss to subluxation of the cervical vertebrae, severe vertebral destruction, and pseudo-ankylosing spondylitis[8]. Other potentially painful complications of upper cervical CPPD involvement include spontaneous fractures of the odontoid process[9] and chronic

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myeloradiculopathy[10,11] due to compression of the proximal spinal cord.

Although painful disorders of the neck and radiological changes of the cervical spine related to this condition have been described, the relationship between CPPD deposition disease and neck pain has not been analyzed explicitly. We conducted a prevalent case-control study to address the hypothesis that the presence of CPPD deposition disease is indeed a risk factor for neck pain.

MATERIALS AND METHODS

Patients with CPPD. All consecutive inpatients diagnosed with CPPD deposition disease of peripheral joints were proposed for inclusion. The inclusion criteron was a diagnosis of CPPD deposition disease according to the criteria set by McCarty[12]. Definite CPPD disease was defined as radiographic evidence of typical calcified deposits involving more than one set of joints and by identification of characteristic CPPD crystals in the synovial fluid. Probable CPPD disease was defined by the presence of either the typical radiographic calcifications or the presence of CPPD crystals in the synovial fluid. Patients were excluded if neck pain was their chief complaint, or if they were unable to answer a short questionnaire or to undergo a computed tomography (CT) scan. All participants provided informed consent. Between February first and July 31, 2002, 37 consecutive patients were diagnosed with CPPD deposition disease of peripheral joints in the rheumatology departments of the University Hospital of Vaud and La Chaux-de-Fonds Community Hospital, Switzerland. Of those, one woman was excluded because her chief complaint was acute neck pain and one man because he did not consent to participate in the study.

Control groups. Two control groups, a radiological control group and a clinical control group, were matched with the CPPD cases by sex and by age, in 5-year sequences. The first group controlled for the CT scan findings: radiological controls were selected among patients investigated by a cerebral CT scan, which was extended to screen the upper cervical spine. The radiological control group included 24 patients investigated for declining cognitive function and by 11 patients with craniocerebral trauma. Because of their neurological condition, they were unable to complete the questionnaire. Therefore a second, similarly matched group was formed to control for the clinical information. The clinical control group comprised 35 patients hospitalized in rehabilitation for various conditions: 12 patients after a stroke, 10 patients after an amputation of a lower limb, 7 patients after orthopedic surgery, 3 patients after heart failure, 1 patient after a craniocerebral trauma, and 1 patient after treatment of a cerebral tumor. Exclusion criteria for all control patients were a known history of CPPD disease, as well as being unable to answer a questionnaire.

Methods. This was an observational study with a matched prevalent case-control design. After informed consent, all patients gave a short history related to the clinical presentations of CPPD disorder, and completed the Functional Rating Index (FRI)[13] questionnaire, a validated questionnaire of subjective perception of pain and function of the spine. Subsequently, a lateral cervical radiography and a non-contrast CT scan of the upper cervical spine were performed. The standard radiographs and the cervical CT scan were graded for OA and for the presence of periodontoid calcifications by 2 independent readers (a radiologist and a rheumatologist). Both assessors were blinded to the disease status of the patients. The mean value of the 2 independent assessments was used for the calculations. The severity of the cervical OA was graded according to the Kellgren & Lawrence classification[14] on the entire cervical spine on lateral radiographs, and for the atlanto-odontoid joint on CT scans. No standard cervical radiographs were available for comparison in the radiological control group. Nevertheless the severity of OA could be compared between the 2 groups on the CT scans of the atlanto-odontoid joint. The periodontoid calcified deposits could be either CPPD crystals or apatite crystals, but they could not be distinguished by radiography. Periodontoid calcified deposits were ranked into 4 stages[6] (Figure 1): stage 1: thin calcifications (< 1 mm); stage 2: thicker curvilinear deposits (> 1 mm) in a single band; stage 3: in a double band; and stage 4: when the TLA was ossified.

Analysis. Because of the small sample size, we collapsed the age-matching sequences into 3 age groups: below age 70, from age 70 to 80, and above 80. For parts of the analysis we decided to dichotomize some outcomes: the neck pain questionnaire was classified as no or minor neck pain (FRI < 10) or presence of neck pain (FRI ≥ 10), and the periodontoid calcifications were classified as no calcified deposits (stage 0) or presence of calcified deposits (stages 1 to 4). Two missing FRI questionnaires of CPPD cases were conservatively considered symptom free and scored zero. To assess the relationship between CPPD and neck pain, we dealt with the presence of CPPD in peripheral joints analytically as a risk factor. We then computed odds ratios (OR) as the odds of neck pain in those with CPPD divided by the odds of neck pain in subjects without CPPD.

The statistical analysis was performed with Stata version 7.0 for Windows. All statistical tests were 2-sided and evaluated at the 0.05 level of significance. For the hypothesis testing, the exact McNemar significance probability test was used for paired data involving proportions and the Wilcoxon signed-rank test was applied for ordinal or non-normally distributed continuous data. Spearman's rank correlation coefficient was used to compute correlations between continuous and ordinal variables. We performed a stratified analysis on the matching factors (sex and age group) and reported the stratified results or a pooled summary measure, whichever was relevant.

RESULTS

Among the 35 CPPD patients included in the study, 14 had definite CPPD deposition disease and 21 had probable CPPD deposition disease according to the criteria of McCarty. Ten of these CPPD cases presented with acute attacks of CPPD gout of peripheral joints, 4 with severe destructive OA, and the remaining 21 consulted for symptoms of OA or for soft tissue pains. In 5 cases an endocrine disorder predisposing for CPPD deposition disease was discovered (3 hemochromatosis and 2 hypothyroidism).

The demographic characteristics of the 3 patient groups were very similar: 35 patients in each group, composed of 21 women and 14 men, with a mean age of 72.7 [standard deviation (SD): 12.6] years for the CPPD cases, 72.3 (SD 12) years for the radiological controls and 72.2 (SD 12.6) years for the clinical controls.

Radiographic results. On the CT scans, periodontoid calcified deposits were observed in 24 patients [69%, 95% confidence interval (CI): 0.52, 0.87] among the CPPD cases, and in 4 patients (11%, 95% CI: 0, 0.23) among the radiological controls (McNemar: $p < 0.001$). The prevalence of periodontoid calcifications remained significantly different among all age groups and in both sexes, but became more important with older age (Figure 2). Overall, periodontoid calcification was 6 times more common among the CPPD cases than among the radiological controls (prevalence ratio = 6, 95% CI: 2.35, 15.3). Among CPPD cases, the extent of the cervical calcifications was as follows: stage 0: 11 patients (31%); stage 1: 3 patients (9%); stage 2: 7 patients (20%); stage 3: 9 patients (26%); and stage 4: 5 patients (11%). The median extent of calcifications was of stage 2 in

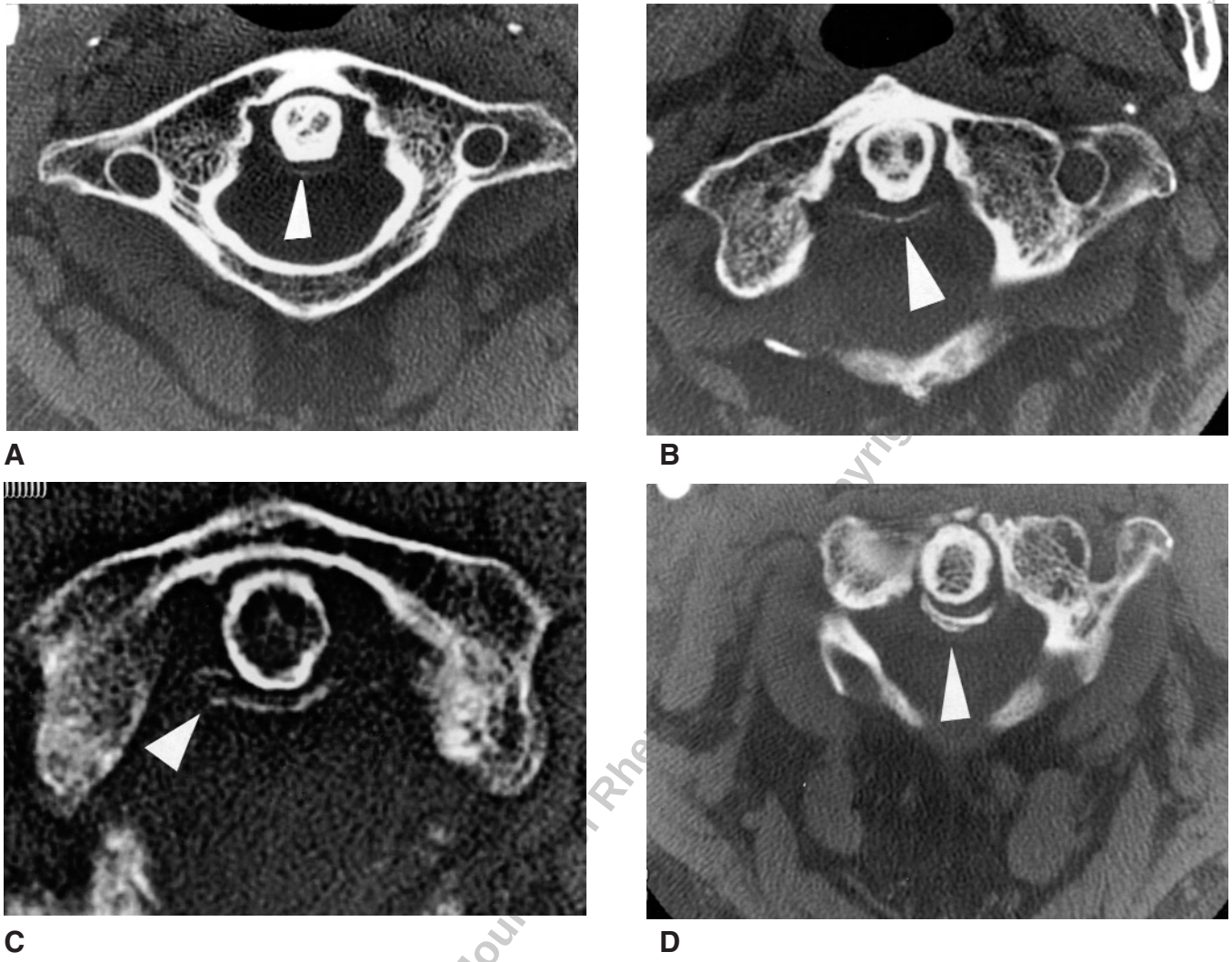

Figure 1. CT scan staging of calcified deposits of the transverse ligament of the atlas (TLA) in order of increasing importance. A: punctiliforme, B: linear, C: double linear, D: ossification.

the CPPD cases as compared to stage 0 in the radiological controls (Wilcoxon signed-rank test: $p < 0.001$). This difference remained significant in all age groups and both sexes.

On the lateral cervical radiographs, calcifications of the intervertebral discs appeared in 16 (48%) patients among the CPPD cases. Most of these patients had also advanced cervical OA, with a median OA grade of 3 on a scale of 4 [interquartile range (IQR): 3 to 4], for the most affected segment. Cervical OA could be compared for the atlanto-odontoid joint. In CPPD cases above 80 years old, the median grade of OA was 3.5 as compared to 2 in radiological controls (Wilcoxon signed-rank test: $p = 0.04$). No statistically significant difference in the severity of OA could be demonstrated in younger patients.

Clinical results. Among the CPPD cases, 3 patients mentioned a past episode of acute or sub-acute attack of neck pain associated with segmentary stiffness, fever, or increased sedimentation rate. When questioned about their current neck symptoms, 12 patients (34%) denied discomfort or pain (FRI < 10), 17 patients (49%) complained of mild pain or dysfunction of their neck (FRI 10-40), and 6 patients (17%) reported moderate to severe pain and dysfunction of their neck (FRI scores > 40). The CPPD cases reported significantly more pain and discomfort of the neck than clinical controls (Figure 3). The median FRI score in CPPD cases was 24 (IQR: 5, 37.5), compared to 2.5 (IQR: 0 7.5) in the clinical controls (Wilcoxon signed-rank test: $p < 0.001$). CPPD cases were 5 times more likely than clinical controls to report any neck pain (OR 5.5, 95% CI: 1.9, 21.9). A moderate correlation was found between the extent of periodontoid calcified deposits and the intensity of neck symptoms (Spearman rank correlation: $r_s = 0.58$, $p = 0.03$) among the male CPPD cases. But among female CPPD cases, radiological findings and neck pain were essentially uncorrelated (Spearman $r_s = -0.3$, $p = 0.18$).

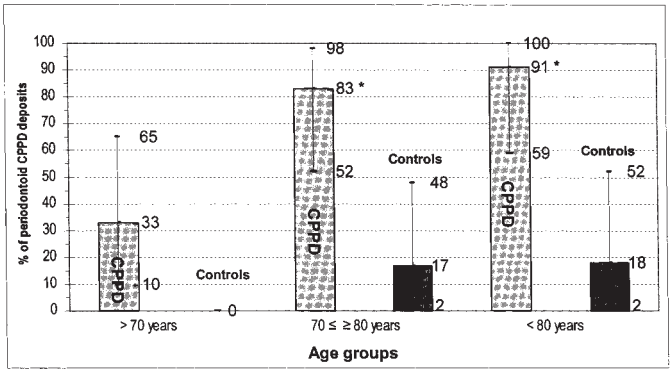

Figure 2. Prevalence of cervical calcifications (periodontoid calcified deposits) among patients with CPPD and radiological controls, in 3 age-groups. *Statistically significant (McNemar's exact: $p < 0.05$).

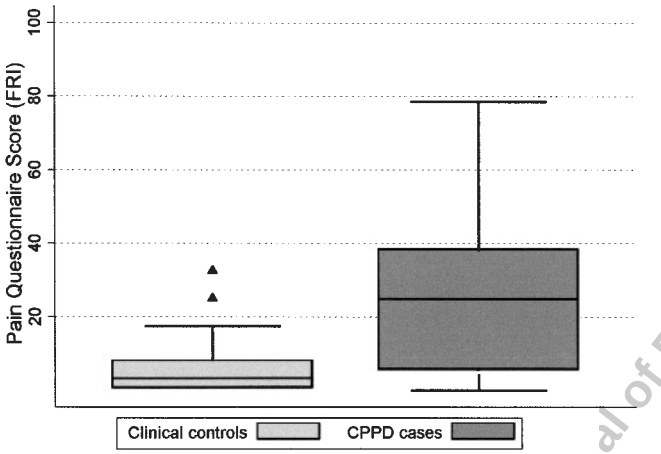

Figure 3. Self-reported pain and dysfunction of the neck (FRI questionnaire score) between clinical controls and CPPD cases. For CPPD cases, the median score was 24 (IQR: 5, 37.5), for clinical controls the median score was 2.5 (IQR: 0, 7.5) (Wilcoxon signed-rank test: $p < 0.01$).

DISCUSSION

We studied 35 patients with CPPD deposits in peripheral joints for signs of CPPD involvement of the cervical spine and for symptoms of the neck. We found that nearly 70% of these CPPD cases also revealed calcified deposits in their upper cervical spine (TLA), as compared to only 11% in the controls. These results are in agreement with those of Constantin[6] who found 66% of calcifications on cervical CT scans, but higher than the results of Dirheimer[15], who reported 44% of calcifications on radiotomography, a less sensitive technique. If we assume that most of these calcifications are in fact CPPD deposits, this would make the TLA one of the prime locations for CPPD deposits. The reason for CPPD's preferential deposition in this location may be related to the structure of the TLA's cartilage. In fact, the TLA is composed mainly of fibrocartilage[16], as are the menisci of the knee, the triangular fibrocartilage of the wrist, and the symphysis pubis, which are the most frequent locations of CPPD deposits. In the radiological control group, 11% of patients also presented calcified deposits in the TLA. This certainly reflects the presence of undiagnosed CPPD deposition disease in elderly patients, since the expected prevalence of CPPD deposition disease in this age group is between 10-20%[1]. Both among CPPD cases and radiological controls, the prevalence of periodontoid calcifications increased with advancing age. Likewise intervertebral disc calcifications of the spine have also been found associated with older age and more severe CPPD disease[3]. Thus calcified deposits of the TLA probably reflect long-standing CPPD disease.

Clinical relevance of the high prevalence of CPPD deposition in the cervical spine is not well established. In our study, the presence of CPPD seemed to be a risk factor for neck pain as CPPD cases reported neck pain significantly more often than the clinical controls (OR 5.5, 95% CI: 1.9, 21.9). This association was further corroborated by the detection of a correlation between the extent of CPPD deposits in the cervical spine and the severity of neck pain among male CPPD cases. Similar findings have been established in peripheral joints such as the knees, the wrists, and the elbows, where it has been determined that the presence of CPPD is associated with more symptomatic OA[17]. Among women in this study, the correlation between neck symptoms and extent of CPPD involvement of the upper cervical spine was not significant. Since other concomitant musculoskeletal disorders tend to be more prevalent among women, they could have confounded this association[18,19].

The mechanism responsible for neck pain in CPPD deposition disease is not clear. It could be related to cervical OA, since increased risk of OA and more severe OA have been associated with CPPD deposition disease[7,20,21]. In fact, we also found a significant association between the presence of CPPD and more severe OA of the atlanto-odontoid joint among patients over 80 years old, but no such association could be established in the younger patients with CPPD. However, the presence of OA did not correlate well with neck pain (results not shown), whereas the presence of cervical calcifications did correlate with neck pain, at least in men, suggesting another mechanism than OA for these symptoms. An alternative plausible explanation could therefore be some low-grade inflammation triggered by the CPPD crystals deposits.

There are clearly some limitations to this study. Since we have a relatively small sample size, only relatively large effects could be detected significantly. Another limitation is the cross-sectional design where CPPD and neck pain are assessed at the same time. However, since the presence of CPPD deposits is a relatively stable condition in time[7,22], we could use the presence of CPPD on the CT scan as a proxy for prior exposure to CPPD crystals to make longitudinal inferences about the effect of this exposure and neck symp-

toms. Nonetheless, in this setting we could not attempt to study the duration of exposure to the CPPD crystals, or the time interval between calcification and the occurrence of neck pain. Still another concern with case-control studies is selection bias. We argued that a proper control disease should have similar referral patterns and be unrelated with CPPD deposition disease or neck pain. This was felt to be adequate with hospital controls in these diagnostic groups. Another limitation of the study is the inability to identify the type of crystals in the calcified deposits of the TLA. Further pathological studies are warranted to confirm the nature of these calcifications. The strengths of this study included the careful matching for potential confounders of this association. Given these limitations, these results should be confirmed by further research in other populations, using study designs that minimize potential selection bias.

We aimed to explore the relation between CPPD crystal deposition disease and neck pain. We confirmed the frequent involvement of the cervical spine in CPPD crystal deposition disease and showed that the presence of calcified deposits in the cervical spine was associated with more cervical pain and dysfunction. This association may be related to more advanced cervical OA, as displayed in the older patients of this group, or related to subacute inflammation caused by the CPPD crystals. Further clinical research is warranted to confirm these findings in a larger prospective cohort study. Better awareness by clinicians of CPPD deposition disease as a cause of acute and chronic neck pain should be stressed, particularly since the therapeutic approach may be different for these patients. Similarly to CPPD gout, it could be worthwhile to start patients with CPPD related neck pain on antiinflammatory medications instead of simple analgesics or physical therapy.

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