Prevalence of Chondrocalcinosis in Patients with Primary Hyperparathyroidism in Japan

TOHRU YASHIRO, TAKAHIRO OKAMOTO*, REIKO TANAKA*, KOHICHI ITO*, HISATO HARA*, TOMOYUKI YAMASHITA*, YOSHIHARU KANAJI*, TAKAYA KODAMA*, YUKIO ITO*, TAKAO OBARA*, AND YOSHIHIDE FUJIMOTO*

Department of Surgery, Institute of Clinical Medicine, University of Tsukuba, Ibaraki 305, and *Department of Endocrine Surgery, Institute of Clinical Endocrinology, Tokyo Women's Medical College, Tokyo 162, Japan

Abstract. One hundred and thirty-two consecutive patients with primary hyperparathyroidism were studied preoperatively for the presence of chondrocalcinosis, the roentgenographic marker of calcium pyrophosphate dihydrate (CPPD) crystal deposition disease, by obtaining radiographs of knees, wrists and pelvis. Chondrocalcinosis was found in 8 patients (6.1%), each of whom was over 50 years of age. In 72 of the patients over 50 years of age, the prevalence of chondrocalcinosis in the hyperparathyroid patients (11.1%) was greater than that found in 72 control patients (2.8%) with thyroid nodular disease who were exactly matched for age and sex, but the difference was not significant. The prevalence of chondrocalcinosis in the hyperparathyroid patients sharply increased with age. In the group in their 50's it was 4.4%, rising to 15.8% in patients in their 60's and reaching 37.5% for those over 70 years of age. Patients with chondrocalcinosis were significantly older than those without this finding (p<0.005). Those with chondrocalcinosis also had significantly higher preoperative serum calcium levels than those without it (p<0.05). While chondrocalcinosis was detected by taking joint radiographs in all patients with primary hyperparathyroidism, acute arthritis (pseudogout attack) occurred in only 2 of the 132 patients (1.5%) after parathyroidectomy, but this represents 25% (2 of 8) of those who had chondrocalcinosis. An attack of pseudogout may therefore be one of the most common postoperative complications of parathyroid surgery in the elderly. Considering the low incidence of pseudogout attack following parathyroidectomy, preoperative radiological studies of the knee joints are sufficient to screen for chondrocalcinosis and are recommended for patients over 60 years old in Japan. Since 25% of patients with chondrocalcinosis will be expected to get acute pseudogout postoperatively, calcium supplement therapy in the immediate postoperative period is recommended for patients with this radiologic finding in order to prevent such an attack.

Key words: Primary hyperparathyroidism, Chondrocalcinosis, Pseudogout attack, Calcium pyrophosphate dihydrate deposition disease, Japan.

CALCIUM PYROPHOSPHATE dihydrate (CPPD) crystal deposition disease, also known as pseudogout, is a disorder that usually occurs in elderly persons sporadically and is characterized by deposits of CPPD crystals in the joints, producing typical radiographic abnormalities called chondrocalcinosis, and a broad spectrum of arthritis syndromes [1]. Primary hyperparathyroidism is known to be associated with CPPD disease and with acute CPPD crystal-induced synovitis (pseudogout attack). Many authors in Europe and USA have reported this association and have

Received: April 19, 1991
Accepted: August 5, 1991
Correspondence to: Dr. Tohru YASHIRO, c/o Dr. Edwin L. Kaplan, Department of Surgery, University of Chicago, Box 402, 5841 South Maryland Ave., Chicago, Illinois 60637, U.S.A.
described the clinical features of a pseudogout attack following parathyroidectomy. However, there are few available reports on such an association in Japanese individuals [2–4]. This study was undertaken to establish the prevalence of chondrocalcinosis, the roentgenographic marker of CPPD disease, in patients with primary hyperparathyroidism in Japan.

Materials and Methods

One hundred and thirty-two consecutive patients who underwent initial cervical exploration for primary hyperparathyroidism were studied preoperatively for radiographic evidence of chondrocalcinosis at the Institute of Clinical Endocrinology, Tokyo Women's Medical College Hospital between 1984 and 1989. The diagnosis of hyperparathyroidism was confirmed by histologic examination (112 patients with adenoma, 14 primary hyperplasias and 6 cancers). There were 92 females and 40 males with an age range from 18 to 81 years (48.0±1.3 years; Mean±SEM). Of the 132 patients, 4 were in their teens, 16 in the 20s, 16 in the 30s, 24 in the 40s, 45 in the 50s, 19 in the 60s, 7 in the 70s, and 1 in the 80s.

It has been demonstrated that CPPD disease is uncommon under the age of 50 in the general population of Japan [5]. Therefore, when we compared the prevalence of chondrocalcinosis in hyperparathyroid patients with that in the general population, we confined the subjects to those over 50 years of age. Seventy-two of the 132 patients (54.5%) were eligible for analysis—65 females and 7 males, mean age 59.2±0.8 years. Seventy-two control subjects who were exactly age- and sex-matched with hyperparathyroid patients were selected from euthyroid patients attending the Institute of Clinical Endocrinology for treatment of thyroid nodular disease.

Radiologic studies were performed as follows. Anteroposterior and lateral radiographs of both knees and anteroposterior radiographs of at least one wrist were taken with standard film for all patients and examined for chondrocalcinosis of the knee joints and the triangular cartilage of the wrist, respectively. An anteroposterior radiograph of the pelvis was also taken in 82 of 132 patients (62%) and examined for chondrocalcinosis of the symphysis pubis. For the control group, radiographs were limited to the knee joints. Chondrocalcinosis was defined as present when one joint showed typical punctate and linear calcifications in the fibrocartilage and/or definite calcification in the hyaline articular cartilage.

The concentrations of serum calcium, phosphate and alkaline phosphatase were determined preoperatively. The serum parathyroid hormone (PTH) level was measured by the radioimmunoassay technique using an antibody specific for the carboxy-terminal sequence of the parathyroid molecule. The serum calcium values were corrected for an albumin level of 4.0 g/dl.

Statistical analysis of the data was performed by Student's t-test, the Cochran-Cox's test, and Odd's ratio. Differences between groups were considered significant if the p-value was less than 0.05.

Results

Eight of the 132 patients with primary hyperparathyroidism had chondrocalcinosis, a prevalence of 6.1% (Table 1). Three of the 8 patients with chondrocalcinosis have been reported before [4]. The prevalence was 0% up to the age of 49 and 4.4% in patients between the ages of 50 and 59. Thereafter, the prevalence increased sharply, rising to 15.8% in patients between the ages of 60 and 69, and reaching 37.5% for those over 70. Thus, all patients in the primary hyperparathyroidism group who were demonstrated to have chondrocalcinosis were over 50 years of age. When the subjects were limited to over 50 years of age, the prevalence of chondrocalcinosis in hyperparathyroid patients increased to 11.1%. In the control group, two females aged 78 and 81 years had chondrocalcinosis, a prevalence of 2.8%. The difference was not significant, however Odd’s ratio = 4.52 (95% confidence interval 0.92-22.20).

The profile of hyperparathyroid patients with chondrocalcinosis is shown in Table 2. The frequency of demonstrable articular calcification in the radiographically examined joints was greatest in the knees (100%). Radiographs of the pelvis were obtained for 5 of the patients and chondrocalcinosis was noted in all 5. Radiographs of the wrists were obtained for all patients and chondrocalcinosis was noted in 5 of them (62.5%). Two patients had a history of joint pain, but none had ever suffered an attack of acute arthritis. The
diagnosis of chondrocalcinosis was therefore first made by taking joint radiographs in all patients. An acute attack of pseudogout occurred in 2 of these 8 patients in the left knee on the fourth postoperative day and in the left hip joint on the third postoperative day, respectively, after removal of a parathyroid tumor. In these two patients who experienced episodes
of acute pseudogout after parathyroidectomy, the serum calcium levels dropped from 11.4 mg/dl and 12.8 mg/dl before operation to 8.3 mg/dl and 8.3 mg/dl on the day of the episode, respectively. On the other hand, in patients with chondrocalcinosis who remained asymptomatic postoperatively, the serum calcium levels dropped from a mean value of 12.13 mg/dl before operation to 8.72 mg/dl within 5 days after parathyroidectomy. The mean postoperative fall in the serum calcium level in these subgroups was almost the same (31.4% versus 29.1%).

The mean age of the patients with chondrocalcinosis (63.3±3.0 years) was significantly (P<0.005) higher than that of patients without this finding (47.0±1.3 years) (Table 3). We found that patients with chondrocalcinosis had a significantly higher (P<0.05) preoperative serum calcium level (12.1±0.2 mg/dl) than those without it (11.3±0.1 mg/dl). A higher preoperative serum calcium level in patients with chondrocalcinosis was also evident when the subjects were limited to over the age of 50 years (12.1±0.2 mg/dl vs. 11.2±0.1 mg/dl, P<0.05). But there was no significant difference in concentrations of the preoperative serum PTH, phosphate or alkaline phosphatase. There was no relationship between the prevalence of chondrocalcinosis in patients with primary hyperparathyroidism and tumor histology.

YASHIRO et al.

Table 4. Reported prevalence of chondrocalcinosis in patients with primary hyperparathyroidism

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Age of patients (years)</th>
<th>% with chondrocalcinosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daddis &amp; Steinbach 1968 [6]</td>
<td>91</td>
<td>Mean 49.6</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>(20)¹</td>
<td>≥50</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>(11)</td>
<td>≥60</td>
<td>73</td>
</tr>
<tr>
<td>Rynes &amp; Merzig 1978 [9]</td>
<td>26</td>
<td>Mean 53.6</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>(9)</td>
<td>≤49</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>(17)</td>
<td>≥50</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>(12)</td>
<td>≥60</td>
<td>67</td>
</tr>
<tr>
<td>McGill et al. 1984 [10]</td>
<td>32</td>
<td>Mean 58.7</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>(16)</td>
<td>≤59</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>(16)</td>
<td>≥60</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>(26)</td>
<td>≤54</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>(40)</td>
<td>≥55</td>
<td>33</td>
</tr>
<tr>
<td>Van Geertruyden et al. 1986 [12]</td>
<td>71</td>
<td>Mean 54.6</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>(26)</td>
<td>≤49</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>(45)</td>
<td>≥50</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>(28)</td>
<td>≥60</td>
<td>50</td>
</tr>
</tbody>
</table>

¹: Number of patients by indicated age-group.
²: Arbitrarily defined age.
³: Incidence of chondrocalcinosis by indicated age-group.
Discussion

It is well known that primary hyperparathyroidism is capable of promoting deposits of CPPD crystals in the joints, and that the prevalence of chondrocalcinosis in patients with primary hyperparathyroidism is higher than that in the general population. While the reported prevalence of chondrocalcinosis in patients with primary hyperparathyroidism varies widely from 3.8% to 40% [6-13], the prevalence in patients over 50 years of age generally exceeds 30% (Table 4). The 6.1% prevalence found in all of our hyperparathyroid patients and the 11.1% prevalence in those over 50 years are among the lowest rates that have been reported. In spite of the higher risk of chondrocalcinosis in patients with primary hyperparathyroidism (about 4 times higher prevalence than in the control), the Odd’s ratio between the hyperparathyroid patients and the control subjects was not significant (95% confidence interval 0.92-22.20). It has been suggested that variations in the age of the study subjects and methods of establishing the diagnosis of chondrocalcinosis account for the wide disparity in prevalence [8]. In addition to these factors, the stage of parathyroid disease is another important factor that may affect such a prevalence. It has been demonstrated that chondrocalcinosis is more common in patients with metabolic bone disease due to primary hyperparathyroidism [6, 8]. This finding probably reflects the fact that these patients had been exposed to hypercalcemia and/or an increased parathyroid hormone concentration for a long time. Approximately 30% of the patients had metabolic bone disease in the previous reports [6, 8]. In our series, patients with asymptomatic and mild hyperparathyroidism diagnosed incidentally by multichannel biochemical screening account for 42% of all subjects, and only 12% of the patients had radiographic evidence of parathyroid bone disease. Furthermore, the mean preoperative serum calcium level in patients without chondrocalcinosis in our study was lower than that reported by any other author [6, 8-10]. These facts indicate that the stage of the disease in our patients was far milder than those referred to in previous reports. Thus, it appears that as the percentage of patients with asymptomatic and mild hyperparathyroidism increases, the prevalence of chondrocalcinosis in patients with primary hyperparathyroidism may also decrease. In addition, ethnic difference may partially account for the wide disparity since the reported prevalence of CPPD disease in the Japanese population seems to be lower than that in Europe or the USA [14].

We found that chondrocalcinosis appeared from the age of 50 in hyperparathyroid patients, and that patients with chondrocalcinosis were significantly older than those without it. These results are similar to those of other studies [8-10]. Furthermore, the prevalence of chondrocalcinosis increases with age in a striking fashion in the group over 50 years. 15.8% of patients in their 60’s and 57.5% for those over 70 exhibited this disorder. On the other hand, chondrocalcinosis occurred rarely in our patients without primary hyperparathyroidism. Only two patients, whose ages were 78 years or older, in the control group in our series had evidence of this problem. The critical age in the general population has been reported to be 65-75 years [5, 8, 15, 16].

Our study confirmed a previous report [10] that hyperparathyroid patients with chondrocalcinosis have significantly higher preoperative serum calcium levels than those without this disorder. This was true in studies of our patients who were over 50 years of age as well. These facts suggest that, in addition to aging, the duration of hypercalcemia may also be important. This opinion is supported by the fact that patients with familial hypocalciuric hypercalcemia, in whom mild hypercalcemia persists throughout one’s life, may also develop chondrocalcinosis [17]. While the serum PTH levels were not significantly higher in patients with chondrocalcinosis in our study, an increased PTH concentration has also been proposed as an important metabolic abnormality which accounts for the accelerated appearance of chondrocalcinosis in the hyperparathyroid state [9, 10].

Chondrocalcinosis is not always the result of deposition of calcium pyrophosphate dihydrate crystals, for calcium oxalate, calcium hydroxyapatite or calcium phosphate dihydrate have each been reported occasionally to be the cause [18, 19]. However, calcium oxalate crystal deposition commonly occurs in patients with end-stage renal disease, and the creatinine clearance values in all patients with chondrocalcinosis in our series were greater than 55 ml/min. Furthermore, the radiographic finding of apatite crystal deposition does not show linear cartilage or meniscal calcification.
as seen with CPPD disease [20]. Thus, it is unlikely that chondrocalcinosis seen in our patients was due to other calcium salts.

Chondrocalcinosis most commonly occurs in fibrocartilage or hyaline cartilage, typically the menisci of the knee, triangular ligament of the wrist, elbow, symphysis pubis and shoulder in decreasing order of frequency. Our radiological studies revealed that chondrocalcinosis was most common in the knee joints, as has been reported previously [8]. Resnick et al. [21] reported that radiographs of the knees alone would detect calcification in 89% of patients with chondrocalcinosis. Although we evaluated the presence of chondrocalcinosis in patients with primary hyperparathyroidism by obtaining radiographs of knees, wrists and pelvis in this study, it is likely that radiography of the knees alone is sufficient to screen for chondrocalcinosis.

None of the patients with chondrocalcinosis in our series had a history of a pseudogout attack, and their diagnoses were first made by taking joint radiographs just before the parathyroidectomy. Although most cases of CPPD disease are asymptomatic, the disease sometimes manifests episodes of acute arthritis (pseudogout attack) simulating gout or septic arthritis. When a patient has CPPD disease associated with primary hyperparathyroidism, the pseudogout attack often develops shortly after parathyroidectomy [3, 13, 22, 23, 24]. In our series, pseudogout attack occurred in only 2 of the 132 patients (1.5%) after parathyroidectomy, but in 2 of 8 (25%) patients who had chondrocalcinosis. The affected joint can be as severely painful, swollen and warm as those of gout [3].

A pseudogout attack following parathyroidectomy is considered primarily to be a consequence of sudden postoperative hypocalcemia which produces CPPD crystal shedding into the joint space and, in turn, causes acute crystal-induced synovitis [25]. Some authors suggest that the decrease in the serum calcium level rather than the absolute serum calcium value is more of a contributing factor in provoking a pseudogout attack after parathyroidectomy [23, 24]. In our patients with chondrocalcinosis, however, neither the decrease in the serum calcium level nor the absolute value for the serum calcium concentration differed in patients with pseudogout from those without it. Perhaps the measurement of changes of ionized calcium levels in blood or joint fluid may offer further information concerning the genesis of an acute pseudogout attack. However, whatever the cause, from a therapeutic point of view we consider the avoidance of a sudden decrease in the serum calcium concentration to be a reasonable prophylactic approach for preventing a pseudogout attack following parathyroidectomy [4]. When chondrocalcinosis is recognized preoperatively, such patients should be carefully observed by frequently measuring the serum calcium level and treated with calcium supplement to prevent the rapid fall in the serum calcium level after parathyroidectomy.

In Europe and the USA the incidence of a pseudogout attack following parathyroidectomy has been reported to be from 3% to 6% [12, 13, 26]. However, only two cases of pseudogout attack following parathyroidectomy have been reported previously in the Japanese literature [3]. We found a 1.5% incidence in our series, which is a higher incidence than that of any other postoperative complications seen following initial parathyroid surgery, such as permanent hypoparathyroidism, recurrent laryngeal nerve injuries and postoperative hemorrhage [27, 28]. Although the association between primary hyperparathyroidism and CPPD disease and pseudogout attacks following parathyroidectomy is not widely recognized in clinical practice in Japan, we assert that pseudogout attack is one of the most common postoperative complications of parathyroid surgery, especially in the elderly. However, considering the low incidence of pseudogout attack following parathyroidectomy, preoperative radiological studies of the knee joints are sufficient to screen for chondrocalcinosis and are recommended for patients over 60 years of age in Japan.

Acknowledgments

We thank Professor Edwin L. Kaplan (Department of Surgery, University of Chicago Hospital) for helpful discussion and Ms. Noreen Fulton and Ms. Joey Czerwonka for their help in preparing the manuscript.
CHONDROCALCINOSIS IN HYPERPARATHYROIDISM

References
