Elevated Parathyroid Hormone 44-68 in Idiopathic Calcium Pyrophosphate Dihydrate Crystal Deposition Disease. Role of Menopause and Iron Metabolism?

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ABSTRACT. ***Objective.*** To examine whether idiopathic calcium pyrophosphate dihydrate (CPPD) crystal deposition disease (CDD) is related to altered parathyroid hormone (PTH) metabolism.

Methods. Forty-two patients with idiopathic CPPD CDD were compared with 67 controls, 33 of whom were matched for age and sex.

Results. Serum PTH 44-68 concentrations were elevated in 29% of patients and were significantly higher in the patients than in their sex- and age-matched controls ($Z = -4.664$, $p < 0.0001$). PTH 1-84 levels were normal. Serum calcium, phosphorus, and ferritin levels were normal, but were significantly higher in the patients. Serum PTH 44-68 levels correlated negatively with serum transferrin in female controls aged ≥ 45 years, and with transferrin saturation in the female patients. Correlation between serum ferritin and age was linear and positive in the former subjects and quadratic in the latter.

Conclusion. Elevated serum concentration of PTH mid-fragments containing the 44-68 region could explain the joint disorders associated with idiopathic CPPD CDD, as shown in genetic hemochromatosis. In female patients the elevation of PTH mid-fragments could be linked to changes in iron metabolism provoked by the menopause. (First Release Dec 1 2007; J Rheumatol 2008;35:315–18)

Key Indexing Terms:
IDIOPATHIC CPPD CRYSTAL DEPOSITION DISEASE
PARATHYROID HORMONE 44-68
MENOPAUSE
IRON METABOLISM

Idiopathic calcium pyrophosphate dihydrate (CPPD) crystal deposition disease (CDD) is a frequent cause of joint disorders after the age of 50 years, especially in women. The lack of a relevant family history and of metabolic disturbances associated with these joint disorders is classically used to distinguish the idiopathic form of CPPD CDD from familial forms and from forms secondary to hyperparathyroidism, hemochromatosis, hypophosphatasia, and hypomagnesemia. However, some earlier studies suggested that certain patients with idiopathic CPPD CDD had elevated serum concentrations of fragments containing the terminal or intermediate regions of parathyroid hormone (PTH)[1-4]. A rise in serum PTH 44-68 concentrations, with no corresponding increase in intact PTH 1-84, was recently described in genetic hemochromatosis[5]. Our aim was to determine whether such a disturbance exists in idiopathic CPPD CDD.

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Accepted for publication October 5, 2007.

MATERIALS AND METHODS

The study involved 42 patients. The diagnosis of CPPD CDD was based on the Ryan and McCarthy diagnostic criteria[6], but patients with isolated subchondral arthropathy were included only if they had osteoarticular changes with a distinctive hypertrophic aspect and distribution compatible with CPPD CDD[7]. The controls were 67 patients (40 with inflammatory rheumatism, 9 with osteoarthritis, 18 with other disorders) in whom joint radiography showed no signs of CPPD CDD. Patients and controls with hyperparathyroidism, iron overload, hypophosphatasia, hypomagnesemia, renal failure, abnormal liver function, advanced rheumatoid arthritis, bisphosphonate therapy, or an uncertain diagnosis were excluded. Thirty-three controls aged 42–71 years were matched for age and sex with 33 patients with CPPD CDD.

An immunoradiometric assay was used to measure PTH 1-84 (Nichols Institute Diagnostics, Paris, France). PTH 44-68 was measured with a radioimmunoassay kit from DiaSorin (Antony, France). The antiserum that was used recognized both intact PTH 1-84 and fragments 39-84 and 44-68, but had far greater affinity for fragment 44-68.

The data were analyzed with StatView IV software. Differences and correlations were considered significant at p values below 0.05.

RESULTS

Descriptive data. The 42 patients with CPPD CDD consisted of 36 women aged 45–81 years (62 ± 10 yrs) and 6 men aged 42–76 years (60 ± 12 yrs). Radiological signs of joint chondrocalcinosis were present in 33 cases (79%). Lesions compatible with subchondral arthropathy were observed in all 42

patients (100%). CPPD microcrystals were detected in 2 of 7 patients examined. According to Ryan and McCarthy[6], 2 cases were "definite," 31 "probable," and 9 "possible." In these latter 9 cases, subchondral arthropathies were characteristic of CPPD CDD[7]. Laboratory data on the 42 patients are shown in Table 1. PTH 44-68 was elevated in 12 cases (29%).

The 67 controls comprised 55 women aged 16–71 years (48 ± 15 yrs) and 12 men aged 32–69 years (48 ± 12 yrs). Their PTH 44-68 values were used to determine reference values, which were 262 ± 45 pg/ml in the 33 controls aged < 50 years and 239 ± 48 pg/ml in the 34 controls aged ≥ 50 years (T = 2.082, p = 0.0413).

Comparative data. In the 33 patients with "subchondral arthropathy + chondrocalcinosis" and the 9 patients with "isolated subchondral arthropathy," the following data were compared: the sex ratio, age, clinical manifestations, number of radiologically involved joints and their severity, and all biological measures. The chi-square test and Mann-Whitney test showed no significant difference between patients with and those without radiological signs of joint chondrocalcinosis. This included the serum PTH 44-68 concentration. The number of patients with elevated serum PTH 44-68 concentrations was 9/33 (27%) in the subchondral arthropathy + chondrocalcinosis subgroup, and 3/9 (33%) in the isolated subchondral arthropathy subgroup.

Of the 33 age- and sex-matched patients, 29 (88%) had a serum PTH 44-68 level higher than their respective controls. The difference was significant by a Wilcoxon paired test (Z = –4.664, p < 0.0001). The mean value and standard deviation were 317 ± 66 pg/ml in the patients and 243 ± 39.5 pg/ml in controls. Serum ferritin levels were higher in the 33 age- and sex-matched patients (120.5 ± 55.2 mg/l) than in the controls (86.8 ± 48.5 mg/l) (Z = –3.359, p = 0.0008). Serum total calcium levels were higher in the 31 assessable patients (2.41 ± 0.1 mmol/l) than in the controls (2.37 ± 0.1 mmol/l) (Z = –2.011, p = 0.0443). Serum levels of calcium ions were higher in the 16 assessable patients (1.22 ± 0.04 mmol/l) than in their 16 controls (1.19 ± 0.03 mmol/l)(Z = –2.651, p = 0.008). Serum phosphorus levels were higher in the 30 assessable patients (1.13 ± 0.20 mmol/l) than in the controls (1.02 ± 0.16 mmol/l) (Z = –2.479, p = 0.0132).

Correlations. In logistic regression analysis of the 109 subjects (42 patients + 67 controls), age and serum PTH 44-68 level were the variables most strongly associated with CPPD CDD (Table 2).

In bivariate analyses, in the 20 female controls aged < 45 years, serum PTH 44-68 levels correlated positively with serum PTH 1-84 levels (R = 0.466, p = 0.0381). In the 35 female controls aged ≥ 45 years, serum PTH 44-68 levels correlated positively with serum ferritin levels (R = 0.455, p = 0.0061), but negatively with serum transferrin levels (n = 22, R = –0.526, p = 0.0120). Multivariate analysis selected only serum transferrin.

In bivariate analyses of the 36 female patients with CPPD CDD, serum PTH 44-68 levels correlated negatively with transferrin saturation (R = –0.354, p = 0.0342).

The age-related variations in the serum ferritin level were different in the female controls aged ≥ 45 years and the female patients, with a simple positive linear correlation in the controls (R = 0.476, p = 0.0039) and a quadratic correlation in the patients (Figure 1).

Table 1. Serum chemistry data in 42 patients with CPPD CDD.

	Reference Range	No. of Patients	Mean ± SD	Minimum	Maximum	No. (%) of Patients with Increase	Decrease
PTH 1-84, pg/ml	10–55	42	28 ± 11	8	49	0	1
PTH 44–68, pg/ml							
< 50 years	172–352	3	401 ± 172	281	598	1	0
≥ 50 years	143–335	39	307 ± 49	214	442	11 (28.6)	0
Total calcium, mmoles/l	2.20–2.63	41	2.42 ± 0.1	2.18	2.65	1	1
Ionized calcium, mmoles/l	1.06–1.31	30	1.23 ± 0.05	1.13	1.35	2 (6.7)	0
Phosphorus, mmoles/l	0.8–1.65	41	1.13 ± 0.18	0.74	1.51	0	2 (4.9)
Iron, μmoles/l	12.5–25	41	14.9 ± 5.2	6	27	1	14 (34.1)
Transferrin saturation, %[8]	20–45	42	25.7 ± 8.7	9	45	0	11 (26.2)
Transferrin, g/liter	2–3.8	37	24 ± 0.32	1.77	3.25	0	1
Ferritin, μg/liter							
Male[8]	30–300	6	165 ± 60.1	81	243	0	0
Female[8]	15–200	36	101.3 ± 50.4	26	197	0	0
Magnesium, mmoles/l	0.65–1.05	30	0.88 ± 0.06	0.73	1.02	0	0
Alkaline phosphatase, units/l	100–290	42	143 ± 51	50	247	0	6 (14.3)
ALT, units/l	10–60	42	17.8 ± 11	6	54	0	10 (23.8)
γ-GT, units/l	10–50	42	19.7 ± 10.4	8	51	1	4 (9.5)
Creatinine, μmoles/l	45–115	42	86.7 ± 12	51	110	0	0

* CPPD CDD: calcium pyrophosphate dihydrate crystal deposition disease. PTH: parathyroid hormone; ALT: alanine aminotransferase; γ-GT: γ-glutamyltranspeptidase.

Table 2. Age and serum parathyroid hormone (PTH) 44–68 levels as explanatory factors of CPPD CDD in 42 patients and 67 controls by logistic regression.

Variable	Coefficient	Standard Deviation	Coefficient/ Standard Deviation	p
Age	0.108	0.026	4.098	< 0.0001
Serum PTH 44–68	0.032	0.007	4.384	< 0.0001
Constant	–15.486	2.920	–5.303	< 0.0001

Log-likelihood = –41.536; R^2 = 0.428. CPPD CDD: calcium pyrophosphate dihydrate crystal deposition disease.

DISCUSSION

Our results in idiopathic CPPD CDD are reminiscent of our previous findings in CPPD CDD secondary to genetic hemochromatosis[5].

The first result — a rise in serum PTH 44-68 concentrations with no corresponding increase in PTH 1-84 — suggests that altered PTH metabolism could play a role in the joint disorders that are observed in both diseases. It must be stressed that the same disorders are also observed in hyperparathyroidism. Experimental data show that a mid-region PTH fragment can have biological activity, such as inducing bone cell proliferation[9], cartilage hypermineralization, and bone formation[10]. These data point to a possible role of an excess of mid-region PTH fragments in subchondral arthropathies. Although normal, serum calcium, ionized calcium, and phosphorus levels were significantly higher in the patients than in the controls, suggesting their possible role in CPPD crystal formation. Similarly, despite the lack of a significant difference between patients and controls, alkaline phosphatase levels were low in 14% of patients, suggesting they could also play a role in CPPD crystal formation. CPPD deposition could also be promoted by preexisting joint damage.

The correlations observed here between serum PTH 44-68 concentrations and iron metabolism measures in postmenopausal women are also reminiscent of results obtained in genetic hemochromatosis[5], despite the absence of iron overload. The results for female controls were clear. The serum ferritin level rose gradually with age, as classically reported[11]. The serum PTH 44-68 level correlated positively with serum ferritin, as in hemochromatosis[5], and negatively with serum transferrin. In multivariate analyses, serum transferrin was the only variable explaining the variations in the serum PTH 44-68 level. Recently, human parathyroid glands and cultured human parathyroid cells were shown to express transferrin receptors[12], and this might account for the relationship between iron and PTH metabolism. The results for the female patients were less clear. The serum ferritin level was significantly higher than in the controls and rose more markedly with age after the menopause, peaking between 60 and 70 years and declining rapidly thereafter. Prospective studies are required to determine whether this decrease is natural or drug-related. The serum PTH 44-68 correlated neither with serum ferritin nor with serum transferrin. In contrast, it correlated negatively with transferrin saturation. Again, prospective studies are required to determine whether changes in parathyroid gland transferrin receptors could explain the different relationship between iron and PTH metabolism in female patients with CPPD CDD, or whether other proteins of iron metabolism have parathyroid receptors and are involved in this relationship.

Finally, prospective studies of male patients are required to identify other mechanisms explaining why serum PTH 44-68

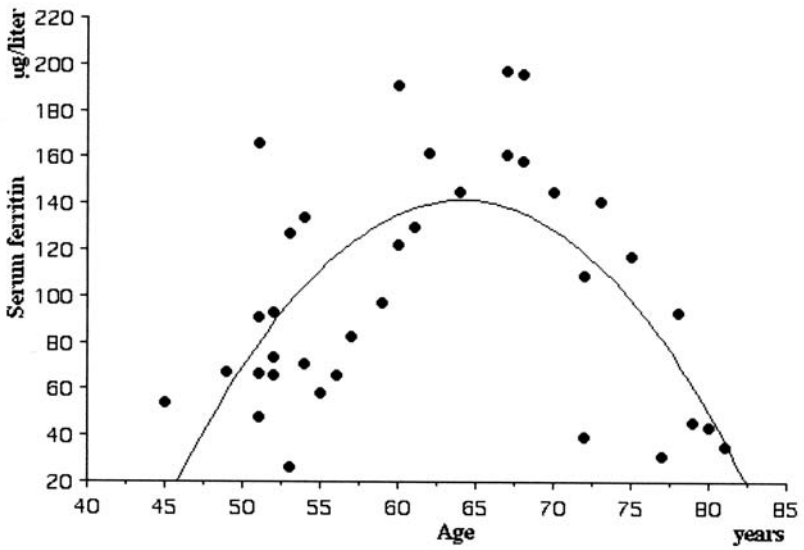

Figure 1. Correlation in quadratic polynomial regression between serum ferritin levels and age in 36 female patients with idiopathic CPPD crystal disease. R = 0.654, p = 0.0001. Age standardized coefficient = 9.651, p < 0.0001. Age^2 standardized coefficient = –9.623, p < 0.0001.

concentrations are elevated whereas intact PTH 1-84 levels are normal.

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