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Case report

Calcium pyrophosphate deposition disease revealing a hypersensitivity to vitamin D

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ABSTRACT

Objective: Hypersensitivity to vitamin D (HVD) due to a loss of function mutation of the *CYP24A1* gene, which encodes vitamin D catabolizing enzyme was initially described as a cause of acute hypercalcemia in children and chronic renal diseases in adults.
Methods: We describe the first case of a patient presenting a calcium pyrophosphate deposition disease (CPDD) revealing a HVD.
Results: An abnormality of phospho-calcic metabolism was discovered during the course of an etiological workup for CPDD in a 52-year-old patient. Laboratory tests revealed a blood calcium level at the upper limit of normal range, a markedly low parathormone level, a 25-hydroxyvitamin D level within the upper level of normal, an elevated 1,25-dihydroxyvitamin D level and an elevated urine calcium level. *CYP24A1* gene sequencing analysis revealed two mutations in a heterozygous state. The study of the 25-hydroxyvitamin D_3: 24,25-dihydroxyvitamin D_3 ratio, two metabolites of vitamin D confirmed the enzyme deficiency in vivo. Our observation suggests that this disease could correspond to a rare cause of CPDD.
Conclusion: In cases of CPDD associated with calcium values within the upper limit of normal range (or hypercalcemia) with an abnormally low PTH, one could suggest searching for HVD.

1. Introduction

Hypersensitivity to vitamin D (HVD), due to a deficit in vitamin D 24-hydroxylase (a catabolic enzyme of 1,25-dihydroxyvitamin D or calcitriol), is an autosomal recessive genetic disease linked to loss of function mutations of the *CYP24A1* gene. The disease is responsible for an accumulation of vitamin D with a dysregulation of intestinal calcium absorption and is characterized biologically by a tendency towards hypercalcemia with low PTH. Clinical manifestations of the disease in children are essentially those of acute hypercalcemia (dehydration, polyuria-polydipsia, nervousness, vomiting). In adults, it is characterized by complications caused by chronic renal hypercalciuria associated with nephrocalcinosis or renal lithiasis.

We describe the case of a patient presenting a calcium pyrophosphate deposition disease revealing a hypersensitivity to vitamin D.

2. Clinical presentation

A 52-year-old patient was hospitalized in the rheumatology department for investigation of an abnormal phospho-calcic metabolism discovered during the course of an etiological workup for calcium pyrophosphate deposition disease (CPDD), which had been progressing since the age of 39 years. He had a typical radiographic articular chondrocalcinosis, pubis radiograph showed calcium deposition in the pubic symphysis (Fig. 1), wrist radiograph showed calcium deposition in the triangular ligament of the right carpus (Fig. 2), knee radiograph showed bilateral calcium deposition in medial and lateral menisci (Fig. 3).

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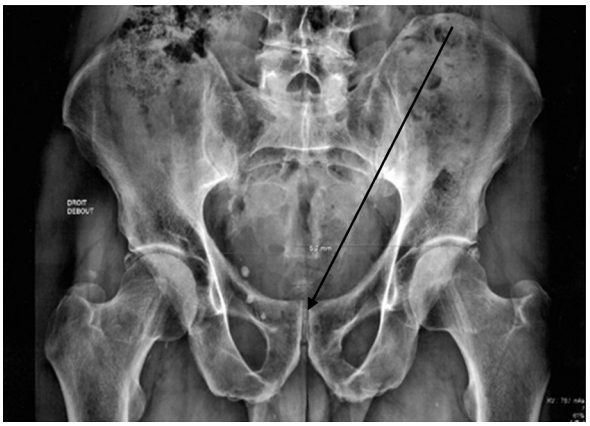

Fig. 1. Calcium deposition in the pubic symphysis.

The patient's past medical history included a monoclonal gammopathy of IgG lambda type and densitometric osteoporosis (T-score –2.91 SD at the lumbar spine, –1.68 SD at the femoral neck). Other medical history included a neurogenic thoracic outlet syndrome with previous surgical intervention and an obstructive sleep apnea syndrome. The patient had no past history of renal disease. The clinical exam was unremarkable, the general condition of the patient was good, and there was no axial or peripheral joint involvement. There was no tumoral syndrome at the clinical evaluation.

Laboratory tests revealed a blood calcium level at the upper limit of normal range (2.6 mmol/L), a markedly low parathormone (PTH) level (6.8 ng/mL), a 25-hydroxyvitamin D level within the upper level of normal although the patient had not received any vitamin D supplement (153.3 nmol/L), an elevated 1,25-dihydroxyvitamin D level (194 pmol/L; normal range, 48–110) as well as an elevated urine calcium level of 8.74 mmol/24 h.

Complementary exploration showed no evidence in favor of granulomatosis (angiotensin converting enzyme and biopsy of the accessory salivary glands were normal), malignant hemopathy (complete blood count normal, plasma protein electrophoresis showed a stable monoclonal peak, sternal bone marrow aspiration

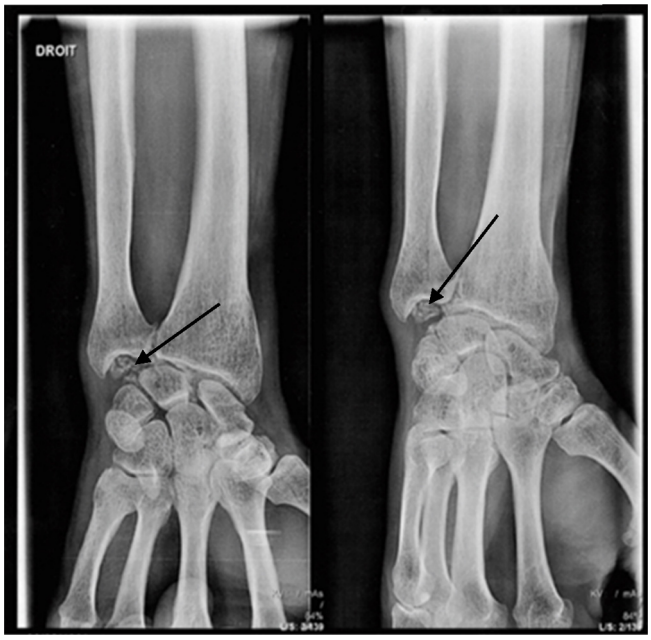

Fig. 2. Right wrist radiograph showing triangular cartilage calcification.

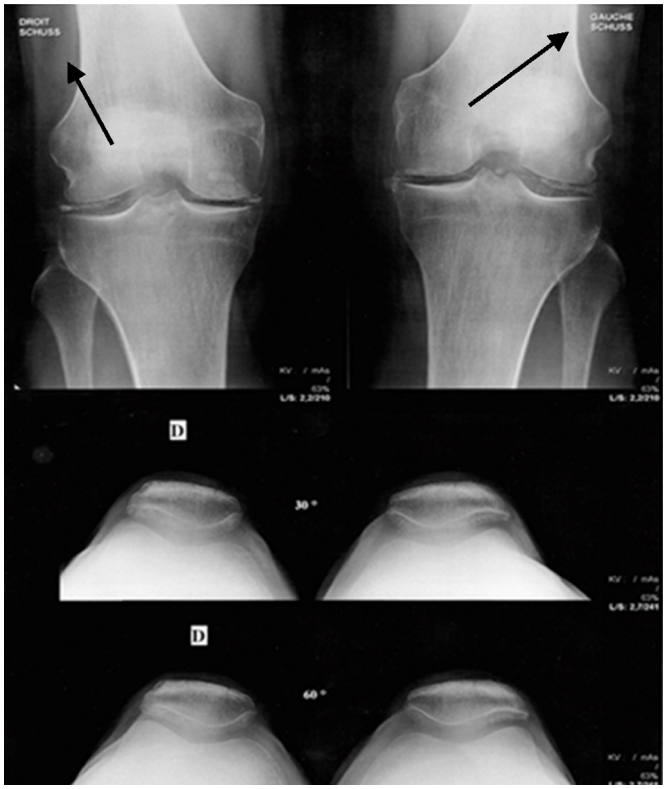

Fig. 3. Knee radiograph showing bilateral meniscal calcifications.

normal), or neoplasia (chest-abdomino-pelvic CT scan and PET-CT scan normal). HLA-B27 typing was positive. The presence of nephrocalcinosis or nephrolithiasis was excluded by the abdomino-pelvic CT scan.

HVD due to a vitamin D 24-hydroxylase deficiency was thus suspected and the patient was given a genetic consultation and a *CYP24A1* gene sequencing analysis. The result revealed the c.427_429del (p.Glu143del) recurrent deletion and a c.62delC (p.Pro21Argfs*8) frameshift mutation, both in a heterozygous state. The study of the 25-hydroxyvitamin D_3: 24,25-dihydroxyvitamin D_3 (25-OH-D_3/24,25-$(OH)_2$-D_3) ratio, two metabolites of vitamin D measured by tandem liquid chromatography coupled with mass spectrometry (LC-MS/MS), confirmed the enzyme deficiency in vivo (25-OH-D_3 = 110.8 nmol/L, 24,25-$(OH)_2$-D = 0.7 nmol/L, ratio = 158).

3. Discussion

To our knowledge, this is the first observation of CPDD associated with HVD due to a vitamin D 24-hydroxylase deficiency that has been documented clinically, radiologically, biologically, and genetically. We have found no publication reporting an association between these two abnormalities; the body of published works to date discusses metabolic and renal consequences of HVD found mostly in children.

Calcium pyrophosphate deposition disease is a crystal-related arthropathy and one of the most common inflammatory joint disease. It is characterized by the presence of calcium pyrophosphate dihydrate crystals within the cartilage of the joints and fibrocartilage [1,2]. The disease is frequent in the elderly, is most often idiopathic, and is not usually found in young persons in which it can occur as secondary to a metabolic disorder [3].

Hence, the most frequent causes of CPDD are primary hyperparathyroidism, haemochromatosis, and hypomagnesemia [4].

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Rarely, genetic causes have been described based on observational studies of databases or clinical case reports. These include familial hypocalciuric hypercalcemia (mutation of the *CASR*) gene [5], familial hypomagnesemia with hypercalciuria and nephrocalcinosis (mutation of the *CLDN16* gene) [6], and familial calcium pyrophosphate deposition disease (mutation of the *ANKH* gene) [7].

Mutations of the *CYP24A1* gene causing hypersensitivity to vitamin D were not identified until recently in children presenting infantile idiopathic hypercalcemia [8]. Since then, there are several clinical cases in adults and a series of adults patients with essentially kidney complications [9–12].

Our observation suggests that this disease could correspond to a rare cause of CPDD. Similar to chronic hypercalcemia resulting from hyperparathyroidism, chronic hypercalcemia linked to HVD could inhibit the chondrocyte alkaline phosphatase and increase the extracellular inorganic pyrophosphate (ePPi) and the formation and deposition of calcium pyrophosphate dihydrate crystals and inflammatory joint disease. It is nevertheless not scientifically sound to state a causality between HVD and CPDD based on only one observation, and other works will be necessary to confirm or dispel this physiopathological hypothesis.

A parathormone level is part of an etiological workup routinely performed for CPDD to detect hyperparathyroidism. Conversely, in cases of association of calcium values within the upper limit of normal range (or hypercalcemia) with an abnormally low PTH, and normal or limit of normal values (or increased) of 25-OH-D_3 and 1,25-$(OH)_2$-D_3, and after exclusion granulomatosis and neoplasias, we would suggest to search for a *CYP24A1* mutation and perhaps to evaluate the 25-OH-D_3/24,25-$(OH)_2$-D_3 ratio [12]. If tests are found positive, the contra-indication of vitamin D supplementation will help to limit the risk of acute and chronic hypercalcemia. The exam is performed on a blood specimen taken after obtaining written informed consent from the patient for a genetic study.

Disclosure of interest

The authors declare that they have no competing interest.

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