Multiple microcrystal deposition within a family

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SUMMARY A family is described in which four members in three generations showed evidence of crystal deposition disease: two developed calcium pyrophosphate dihydrate (CPPD) crystal deposition, one calcific periarthritis, and one mixed crystal deposition disease (gout + chondrocalcinosis). This previously undescribed observation supports a possible role for non-specific heritable connective tissue factors in predisposing to crystal deposition.

Key words: chondrocalcinosis, calcific periarthritis, gout, pyrophosphate arthropathy, calcium pyrophosphate dihydrate crystal deposition disease, familial crystal deposition, mixed crystal deposition.

Familial predisposition has been reported independently for monosodium urate monohydrate (MSUM) crystal deposition in gout,¹ calcium pyrophosphate dihydrate (CPPD) crystal deposition in pyrophosphate arthropathy,² and carbonated apatite (basic calcium phosphate) deposition in idiopathic chondrocalcinosis³ and calcific periarthritis.⁴ The mechanisms of crystal deposition in these diseases, however, are poorly understood, and the genetic factors that enhance susceptibility have not been determined.

We report a family in which all three of the major crystal deposition diseases are represented in different family members. Such an observation supports a role for non-specific heritable connective tissue factors concerned with crystal nucleation and growth in predisposing to crystal deposition diseases.

Case reports

The index case was an 83-year-old Caucasian woman (patient 1) who presented with chronic bilateral gonarthrosis. Symptoms had started 30 years before but had worsened and become persistent over the previous five years. Examination showed a fit woman with no evidence of systemic disease. Both knees were stable but showed varus deformity, quadriceps wasting, patellofemoral cre-

pitus, effusion, and restricted flexion. Additional joint involvement included bilateral Heberden's nodes, non-tender enlargement of both second and third metacarpophalangeal joints, 'squaring' of both first carpometacarpal joints, restricted movement with crepitus of right shoulder and left subtalal joints, and bilateral hallux valgus. Fluid aspirated from both knees was viscous, with total white cell counts of 18 000/mm³ ($18 \times 10^9/l$), 70% neutrophils (right knee) and 16 000/mm³ ($16 \times 10^9/l$), 60% neutrophils (left knee); polarised microscopy in each instance showed triclinic crystals 2-10 μm in length with positive birefringence and inclined extinction consistent with CPPD. Knee radiographs showed bilateral chondrocalcinosis with changes typical of pyrophosphate arthropathy (Fig. 1). Changes of pyrophosphate arthropathy, without chondrocalcinosis, were also marked in both shoulders and present in all other clinically involved joints; chondrocalcinosis as an isolated abnormality was present in the left acromioclavicular joint and in both wrist triangular ligaments. Radiographs of thoracolumbar spine and pelvis showed only moderate spondylosis. Laboratory investigations included normal full blood count and plasma viscosity; serum was negative for rheumatoid and antinuclear factors, and screening of serum calcium, phosphate, alkaline phosphatase, urea, magnesium, iron, uric acid, sugar, and thyroid function excluded underlying metabolic or endocrine disease.

The diagnosis was primary generalised osteoarthritis with pyrophosphate arthropathy. Symptoms and mobility were improved by joint aspiration.

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Fig. 1 Lateral and anteroposterior knee radiograph of index case (patient 1) showing calcification of hyaline and meniscal cartilage, with joint space narrowing, sclerosis, and exuberant new bone formation, predominantly affecting the patellofemoral compartment.

physiotherapy, and analgesic anti-inflammatory drugs.

Enquiry into the family history suggested a high incidence of joint disease with symptoms in her son, one daughter, and her only grandchild (her one other daughter had complained of no joint symptoms and had died of cancer at age 47). Surviving family members were therefore contacted and investigated.

Patient 1's 67-year-old son (patient 2) had a 24-year history of classic acute gout affecting at various times both first metatarsophalangeal joints, knees, ankles, and right wrist. One knee and one ankle had been aspirated during acute episodes and had shown sterile fluid with needle-shaped negative-birefringent crystals consistent with MSUM. Hyperuricaemia had been repeatedly observed despite successive treatments with sulphinpyrazone 600 mg daily (eight years) and allopurinol 300 mg daily (five years). At age 66 he had developed a lymphoma associated with an IgM paraprotein, for which he

received combination chemotherapy. Examination showed an ill man with florid lymphadenopathy: there were no tophi and no evidence of chronic arthropathy. Knee radiographs showed bilateral chondrocalcinosis with medial joint space narrowing (Fig. 2); radiographs of hands, pelvis, and shoulders were normal. Serum urate was 0.6 mmol/100 ml (normal 0.12–0.46 mmol/l), serum urea and electrolytes were normal, and biochemical screening showed no additional metabolic or endocrine disease. Because of his poor general condition knee aspiration was not attempted.

Patient 1's 59-year-old-daughter (patient 3) had a five-year history of intermittent pain, stiffness and swelling of both knees. Examination showed joint line tenderness, effusion, and restricted flexion of both knees; there was no local or generalised hypermobility, and the remainder of the examination was normal. Knee aspiration yielded viscous fluids with total white cell counts of 17 000/mm³ (17×10⁹/l), 60% neutrophils (right knee) and

Fig. 2 Anteroposterior knee radiograph of patient 2 showing hyaline and meniscal chondrocalcinosis in both tibiofemoral compartments, with medial joint space narrowing.

12 000/mm³ (12×10⁹/l), 75% neutrophils (left knee); polarised microscopy of both samples showed triclinic crystals 4–10 µm in length with positive birefringence and inclined extinction consistent with CPPD. Knee radiographs showed medial and patellofemoral compartment osteoarthritis but no chondrocalcinosis; radiographs of hands, shoulders, pelvis, and thoracolumbar spine were normal. Laboratory screening showed no associated metabolic or endocrine disease.

Patient 3's 32-year-old daughter (patient 4) had a history of acute 'gout' at age 12. Examination of

hospital records confirmed the history of spontaneous acute onset of pain, swelling, and erythema of her left forefoot, maximal around the first metatarsophalangeal joint. Although radiograph had since been destroyed, the x-ray report commented on indistinct granular opacification medial to the first metatarsophalangeal joint. Surgical exploration had shown chalky periarticular detritus which was removed; histology of the scrapings was reported as 'crystalline calcific material'. The episode subsequently settled and a repeat x-ray four weeks later was reported as normal. Examination of patient 4 at age 32 showed no abnormality. A radiographic survey showed no periarticular articular calcification.

There were no other living family members. The family tree, with disease distribution and HLA tissue typing, is shown in Fig. 3.

Discussion

Within this family a diagnosis of crystal deposition disease was clearly established in four of five (i.e. all four surviving) first degree relatives, two having pyrophosphate arthropathy, one gout with chondrocalcinosis, and one calcific peri-arthritis. Synovial fluid examination permitted crystal identification in three cases (CPPD in two, MSUM in one). In the patient with gout (patient 2) radiographic chondrocalcinosis was evidence of additional crystal deposition, most probably of CPPD or basic calcium phosphate.⁵ Pyrophosphate arthropathy without chondrocalcinosis is well described⁶ and does not detract from the diagnosis in the case of patient 3.

Fig. 3 Pedigree of family showing HLA phenotype and disease distribution.

Although the diagnosis of calcific periarthritis in the youngest family member (patient 4) was necessarily presumptive, the recorded clinical, radiographic, and histological findings are characteristic of the condition, and no other diagnosis seems tenable. It would therefore appear that all three major crystal deposition diseases are represented within this family. As far as we are aware this is the first report of such an occurrence. Although familial clustering of these conditions could have arisen by chance, the rarity of calcific periarthritis and hereditary CPPD deposition suggests more than coincidental association.

Although hereditary predisposition has been described independently for gout,¹ CPPD crystal deposition,² calcific periarthritis,⁴ and idiopathic chondrocalcinosis,³ the familial factors that lead to crystal deposition in these conditions have not been fully defined. Heritable abnormalities of metabolism that lead to solute excess have been clearly shown in gout⁷ and reported in familial pyrophosphate arthropathy.⁸ The possibility that additional, non-specific crystal promoting factors may also have a role, however, is suggested by the low incidence of gout in hyperuricaemic subjects,⁹ the increased association between gout and chondrocalcinosis,¹⁰ the occurrence of mixed deposition of different crystal species within individuals,¹¹ and the negative association between rheumatoid disease and both MSUM¹² and CPPD¹³ deposition.

The importance of factors with inhibitory or promoting effects on crystallisation has particularly been emphasised in connection with normal bone mineralisation and dentition,¹⁴ urolithiasis,¹⁵ gall stone formation,¹⁶ salivary calculi,¹⁷ and pancreatic calcification.¹⁸ In articular tissues factors incriminated in the control of crystal nucleation and growth, particularly of apatite, include inorganic pyrophosphate, matrix vesicles, collagens, mitochondria, acidic phospholipids, γ -carboxyglutamic acid (GLA)-containing protein, and proteoglycan aggregates.¹⁹⁻²¹ There is little direct evidence, however, of genetic variability in these factors to account for disease susceptibility. Familial variation in local tissue factors, reflected by uronic acid turnover, has been proposed as a major determinant of MSUM deposition in primary gout,²² and abnormality of matrix proteoglycan has been reported to predate CPPD deposition in familial pyrophosphate arthropathy.²³ Facilitation of CPPD deposition by unidentified factors that accompany joint damage and repair is suggested by frequent association with osteoarthritis and by occurrence of localised CPPD deposition in situations of previous joint injury.^{13 24} Similar predisposition to MSUM crystal deposition

could in part explain the preferential involvement of Heberden's nodes and osteoarthritic interphalangeal joints in diuretic-induced gout²⁵ and predilection for the first metatarsophalangeal joint (the earliest and most common site of radiographic osteoarthritis) in primary disease.²⁶ Although positive association between crystal deposition diseases might be explained by epitaxial phenomena, further investigation of factors that promote or inhibit crystal deposition would seem warranted.

The importance of 'soil' as well as 'seed' is further supported by the present observation of multiple deposition of chemically dissimilar crystals within individuals of the same family. In this situation heritable connective tissue factors may be important in permitting development of disease, whereas interaction with additional familial or environmental factors (e.g., hyperuricaemia, generalised osteoarthritis, trauma) may determine the nature and distribution of the crystal deposit.

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