Hereditary disorders mimicking and/or causing premature osteoarthritis

Géza Bálint MD, DSc
Director

Béla Szébenyi MD
Consultant Rheumatologist

National Institute of Rheumatology and Physiotherapy, Budapest, Hungary

Osteoarthritis is the most common joint disease, causing considerable disability and impairment of quality of life. Hereditary osteochondrodysplasias and some inborn errors of metabolism may mimic or cause premature osteoarthritis. Osteochondrodysplasias usually cause joint deformities, such as coxa vara or genu varum, which can cause abnormal biomechanics. In most of these disorders, the articular cartilage is originally defective as a result of genetically determined collagen or matrix protein abnormalities, or the deposition of mucopolysaccharides. In the case of inborn errors of metabolism, the pathological process affects healthy articular structures, causing secondary osteoarthritis. In alkaptonuria, the pathological deposition of polymerized homogenistic acid causes defective changes in cartilage, articular capsule and tendons. In Wilson’s disease, the premature osteoarthritis might be caused by the copper deposition. It is worth paying attention to these rare disorders, even when they are mild or incomplete, because early diagnosis can lead to prevention and effective treatment. In addition, research is discovering the specific gene defects and molecular abnormalities that are responsible for disease expression. This may in turn lead to opportunities for prenatal diagnosis; thus, genetic counselling and gene replacement therapy may be a realistic possibility in the near future.

Key words: premature osteoarthritis; hereditary osteochondrodysplasias; ochronosis; Wilson’s disease; familial chondrocalcinosis.

INTRODUCTION

Osteoarthritis (OA) is a very common disease, usually affecting people over the age of 50. When it develops earlier, in the third or fourth decades of life, it is most often caused by genetic predisposition or one of the causes of secondary OA. In children, teenagers or young adults, hereditable osteochondrodysplasias may cause joint deformities or contractures that can mimic OA, juvenile chronic arthritis (JCA) or rheumatoid arthritis (RA). In these disorders, both the abnormal cartilage and the mechanical factors predispose to premature OA. In the inborn errors of metabolism discussed below, the development and structure of the joints and cartilage is initially
normal. The cartilage and articular defects develop later, but still at a young age, as in ochronosis and haemochromatosis.

Clinical significance of premature OA

The clinical significance of diagnosing uncommon disorders causing premature OA is wide-ranging:

1. A clinical analysis of possible aetiological factors may detect heritable disorders (i.e. formes frustes of chondrodysplasia). In this case, genetic counselling, enabling prevention at the familial level, is important.
2. In the pre-arthriotic stage or in early disease, occupational counselling, a change of lifestyle, patient education and physiotherapy, especially exercise, may prevent the development or progression of OA.
3. In some cases, specific treatment is already available or near to clinical use, for example d-penicillamine treatment in Wilson’s disease\(^5\) and enzyme replacement therapy for mucopolysaccharidoses\(^6\) or immuno-osseous dysplasias.\(^7\) Even gene therapy will probably be available for some disorders in the near future.\(^8,9\)
4. The surgical correction of any abnormal anatomy causing joint overload, such as osteotomy for correcting a varus or valgus deformity of the knee, may prevent or postpone the development of OA.
5. For treating early, premature OA, the transplantation of osteochondral tissues or cells of chondral origin (mesenchymal stem cells and/or perichondral cells) is possible\(^10,11\); cartilage transplantation (e.g. the Hangodi mosaic plastic) can also be performed by arthroscopy.\(^12\)
6. Although we still do not have any real structure-modifying drugs for OA, some may be available in future, which might be used also for these disorders.

HERITABLE OSTEOCHONDRODYSPLASIAS

Classification

The international classification of heritable osteochondrodysplasias defines them as developmental disorders of chondro-osseus tissue, while dysostoses are disorders of single bones.\(^13\)

The international classification of osteochondrodysplasias was worked out by the International Working Group on Constitutional Diseases of Bone in 1991.\(^13\) In spite of the rapid progress of biochemistry, molecular biology and information on gene localization and defective proteins, the Working Group still felt that current aetio-pathological knowledge was too fragmentary to allow for a causal classification. The classification is thus based on radiodiagnostic criteria grouping morphologically similar disorders.

There are lethal forms among these diseases, the sufferers of which do not survive infancy or childhood, and also diseases not complicated by early OA. In this chapter, we will discuss only the most common disorders mimicking or causing premature OA.

Aetiology and pathogenesis

The aetiology and pathological mechanism of premature OA in this group of diseases is twofold.
The abnormal bone and joint anatomy characteristic of these disorders (epiphyseal and metapophyseal dysplasia, coxa vara and valga, and genu varum and valgum) predisposes to the overload of some joints. The cartilage and subchondral bone are often also defective, especially as a result of mutations in the COL2A1 gene, resulting in the production of abnormal type II collagen, which is well established in some of these disorders.\textsuperscript{14,15} Mutations in the gene coding for cartilage oligomeric matrix protein (COMP) cause pseudochondrodysplasia (PSACH) and multiple epiphyseal dysplasia (MED); those in the fibroblast growth factor receptor-3 (FGFR3) result in achondroplasia.\textsuperscript{17} The storage of different mucopolysaccharides in bones and joints, characteristic of the dysostosis multiplex group, which includes mucopolysaccharidoses\textsuperscript{18}, also produces defective cartilage.

Mutations in the gene responsible for the production of type X collagen, expressed in the hypertrophic zone of calcifying cartilage and the main type of collagen in the growth plate, cause Schmid-type metaphyseal dysplasia.\textsuperscript{19} Mutations in other genes responsible for the production of other minor collagens, such as types IX and XI, also play a role\textsuperscript{20,21} in the causation of chondrodysplasias. Gene mutations in parathyroid hormone (PTH) and its related peptide (PTHrP) receptor\textsuperscript{22} play a central role in the development of enchondral bone, a delay in chondrocyte differentiation and a failure of normal mineralization.\textsuperscript{22} The inactivating mutation in the PTH/PTHrP receptor results in Blomstrand chondroplasia, a lethal form of this disease\textsuperscript{23}, and in Jansen-type metaphyseal chondrodysplasia.\textsuperscript{24} The PTH/PTHrP receptor is a member of the class II subfamily of G-protein-coupled receptors (GPCRs).\textsuperscript{22} G-proteins are trimeric guanine nucleotide-binding proteins relaying signals from more than 1000 receptors to many intracellular effectors, including enzymes and ion channels.\textsuperscript{25}

These new genetic and molecular biological research results might enable a better understanding of some forms of primary idiopathic OA. A linkage between the COL2A1 gene and the development of OA has been demonstrated in several families.\textsuperscript{26} Some of these cases of COL2A1-linked familial OA displayed mild chondrodysplasias\textsuperscript{27}, emphasizing the fact that mild forms of chondrodysplasias causing premature OA might not be recognized in clinical practice. Although mutations of the COL2A1 gene responsible for the development of early familial OA may have an aetiological role in only 2\% of OA cases, genetic influence in OA, based on a large-scale twin study, has been estimated to be between 50\% and 65\%.\textsuperscript{28,29} There are certainly some other heritable factors. Wright et al\textsuperscript{30} found an association between nodal OA and two loci on the short arm of chromosome 2 (2q23–35). Keen et al\textsuperscript{31} suggested a relationship between polymorphism of the vitamin D receptor and early knee OA and osteoporosis. The role of a defective production of COMP causing MED end PSACH has not yet been investigated in OA.

On the other hand, various types of chondrodysplasia – some forms of chondrodysplasia punctata – environmental factors such as maternal warfarin use in early pregnancy\textsuperscript{32} and maternal alcoholism, cause embryopathies.\textsuperscript{33} Chondrodysplasia punctata may also be associated with maternal systemic lupus erythematosus.\textsuperscript{34}

**Clinical aspects of heritable osteochondrodysplasias**

This group includes a large number of diseases, about 150, of which several cause arthritis.\textsuperscript{35} Some of them are not very rare, such as achondroplasia (with an incidence of 1 in 25 000 live births\textsuperscript{36}) and Stickler’s syndrome, which (with an incidence of 1 in 10 000 live births) is surprisingly common.\textsuperscript{35} All these diseases cannot be described in this chapter, the aim being to alert the clinician to the possibility of these disorders
when being presented with premature OA with unusual features, only the most important ones being discussed in detail here. One certainly needs a visual knowledge of the physical and radiological characteristics of these diseases to recognize them, the excellent publications by McKusick37, Spranger et al38, Wynne-Davis39, Wiedemann et al40, Maroteaux41 and Bailey42, and the corresponding chapters of Resnick’s excellent radiology textbook43,44, being recommended for this. Audiovisual aids for diagnosis may be developed for main paediatric, orthopaedic and rheumatology departments. An increased number of international centres with experience in diagnosis and treatment for consultation and even surgical referral is of the utmost importance.

Importance of proper diagnosis

The proper diagnosis of chondrodysplasia, especially in patients surviving childhood and in the milder formes frustes, is of growing clinical importance, for the reasons listed above. Some important points with regard to this group of diseases can, however, be mentioned here:

1. Prenatal diagnosis, using either genetic or imaging methods, is possible in most of the disorders.
2. A recognition of these disorders from external body features and radiographs helps to detect the other associated features, such as eye involvement, hearing loss, obstructive sleep apnoea, cardiac disease, immune deficiency, atlanto-axial instability, a narrow spinal canal and mental retardation. These features may not be apparent, but they are of great clinical importance: obstructive sleep apnoea may be fatal; the non-recognition of atlanto-axial instability may result in compression of the medulla or spinal cord. It is essential for the anaesthesiologist, when choosing the most suitable method of anaesthesia for patients requiring any kind of surgery, to know of the presence of atlanto-axial instability, as it is for the treating physiotherapist.

Diagnostic features and clues

Short stature or dwarfism of hypophyseal, renal, cardiac or hepatic origin is always proportionate; disproportionate short stature should always raise the suspicion of osteochondrodysplasia. Short stature can be caused by:

1. relatively short limbs, especially legs, with a relatively long trunk (short leg short stature);
2. a short trunk, mostly due to flat and wedging vertebrae causing kyphosis or kyphoscoliosis, with relatively long limbs (short trunk short stature).

Types of limb shortness can also be differentiated:

1. rhizomelic shortness, when the proximal parts of the extremities (the upper arms and thighs) are relatively short;
2. mesomelic shortness, in which the distal areas (forearms and lower legs) are shorter;
3. micromelic shortness, the hands and feet being relatively short.

Short limb short stature can be recognized in practice when the tip of the third finger reaches only as far as the trochanter region, instead of the mid-thigh, in a normal standing position. The ratio of the lower segment of the body (distance from
the pubic symphysis to the floor) and the upper segment of the body (total height minus lower segment) is less than 0.91 (± 0.004).

The head and face are in many cases characteristic: the relatively large, elongated head with coarse facial features in classical achondroplasia; depressed nasal root and hypertelorism in many of the osteochondrodysplasias; facial dysmorphism in some of the mucopolysaccharidoses. Cleft palate, visual and hearing disturbances and mental retardation are also of diagnostic importance. In some forms, the head and facial features are normal, and no other stigmata and no additional accentuation of the disproportionate short stature can be observed.

Increased lumbar lordosis, and in the short trunk short stature form also kyphoscoliosis with chest deformity, can be marked. A waddling gait usually reflects hip joint disorder. Genu varum or valgum and elbow and finger contractures are also noticeable.

With regard to the radiology, pelvic X-ray abnormalities of the iliac bones (iliac flaring, hypoplasia of the iliac wings, and iliac horns), the acetabula and the femoral heads and necks (acetabular dysplasia, protrusion, femoral head deformities, coxa valga and coxa vara) should be sought. On spinal films, flattening and wedging of the vertebral bodies, irregularities of the vertebral end-plates, a narrow spinal canal and irregularities of the odontoid process with atlanto-axial instability should be noted. Anterioposterior and lateral films of the knee, femora and tibia are often useful, films of other affected areas and the skull sometimes also being necessary.

Laboratory investigations are helpful in diagnosing mucopolysaccharidoses by measuring the urinary output of mucopolysaccharides, in hereditary forms of rickets and in hyper- and hypophosphatasia.

The most important osteochondrodysplasias causing premature OA

*Multiple epiphyseal dysplasia (MED)*

MED is characterized by the abnormal ossification of multiple epiphyses, leading to irregular articular surfaces and premature OA, especially of the hips and shoulders.\(^{45}\)

*Aetiology.* It has been recently proved that novel and recurrent mutations of the calcium-binding domains of COMP, a large, extracellular matrix protein in the matrix surrounding the chondrocytes, may cause either MED or PSACH.\(^ {46}\) Mutations in the seventh calmodulin-like repeat cause severe PSACH while mutations elsewhere in the gene lead to mild PSACH or MED phenotypes.\(^ {46}\) These genotype–phenotype correlations may facilitate the molecular diagnosis and classification of PSACH and MED. The clinical and radiological features of MED are summarized in Table 1. Treble et al\(^ {47}\) analysed the development of the hip in 42 patients with MED. They found two types of hip: first, one with a severely deformed femoral head and acetabular dysplasia, OA developing before the age of 30, and second, a milder form with less deformation, no acetabular dysplasia and a lesser tendency to premature OA. In some cases, aseptic necrosis also occurs. Unlike Legg–Perthes–Calvé disease, MED affects both hips. The expression of the disease differs between families, ranging from 15% to 100%. The type of disease is characteristic of the particular family, and a prediction can be made of the likelihood of premature OA by studying the family history and X-rays of children and adolescents. Severe osteochondritis of the knee in MED has been also described.\(^ {48}\)
**Pseudoachondroplasia (PSACH) group**

PSACH is characterized by short limb short stature, normal facial features, knocking knees, joint laxity, platyspondyly and premature OA. The clinical and radiological features are shown in Table 2.

**Aetiology.** PSACH is inherited as an autosomal dominant trait. It has recently been shown that MED and PSACH are caused by mutations in the gene encoding COMP. An increasing range of mutations causing PSACH and MED has been reported.16

**Achondroplasia and hypochondroplasia group**

Achondroplasia is the best known and most common form of chondroplasia, characterized by short limb, short stature a relatively big skull and with mid-face hypoplasia. The limb shortness is of the rhizomelic type, the proximal sections – the upper arms and thighs – being most shortened.36,50

Hypochondroplasia is a milder condition, with normal facial features and head. This is probably a different disorder with some familial overlap.50

**Aetiology.** Both disorders are inherited as an autosomal dominant trait, with full penetrance in achondroplasia. Mutations of the FGFR3 gene on the short arm of chromosome 4 have recently been found to be responsible for both diseases. Two point mutations (G1138A or G1138C) cause most cases of achondroplasia.51 Eighty per cent of all cases are new mutations arising on the allele derived from the father.52

Hypochondroplasia is usually cased by N540K mutations of the FGFR3 gene. Matsui et al.50 have shown a correlation between the genotype and phenotype, with some phenotypic overlap between the two conditions.

**Clinical features.** The characteristic features of achondroplasia and hypochondroplasia are shown in Table 3.

Achondroplasia is not such a harmless entity as it was previously thought. Its overall mortality is double that of the general population, most of it appearing in early childhood.53 Childhood deaths are mostly caused by atlanto-axial instability and the small foramen magnum, leading to cord compression, sleep apnoea, hydrocephalus and paraparesis. The criteria for surgical decompression are currently the subject of much debate. Recurrent otitis media is very common and frequently leads to conductive hearing loss.54

**Treatment.** Regarding musculoskeletal symptoms and signs at later age, the consequences of a narrow spinal canal are many, requiring surgical decompression.

The contracture of the elbow, the waddling gait and the genu vara with joint laxity mimic OA, although premature OA develops infrequently. Osteotomy is often recommended to correct tibial bowing.54

Seiko et al.51 treated 145 patients with achondroplasia in childhood with growth hormone: a significant dose-dependent effect on skeletal growth was obtained, with no long-term adverse effects. Ramaswami et al.55 treated children with hypochondroplasia with growth hormone. From their experience, it can be seen that only patients failing to develop a growth spurt at puberty should be treated.
### Table 1. Epiphyseal dysplasias.

<table>
<thead>
<tr>
<th>Designation or eponym</th>
<th>Head and face, stature and proportions</th>
<th>Joint and spinal involvement</th>
<th>Radiology</th>
<th>Mental status and extraskeletal manifestations</th>
<th>Inheritance</th>
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<th>Gene</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysplasia epiphysealis multiplex</td>
<td>Head relatively big, otherwise normal, short or normal stature, short legs, relatively long arms, stubby hands and feet, waddling gait</td>
<td>Hips, knees (genu varum, hypoplastic and irregular double patella, chronic dislocation of the ankles (tibiotalar slant), shoulders, elbows (flexion contracture) and spine in more than 60% resembling mild Scheuermann’s disease, scoliosis</td>
<td>Joint incongruity, flattened femoral heads and condyles, hypoplastic double patella, proximal end of the tibia is squared, talar surface is flat, short and broad phalanges, wedge-shaped vertebrae, platyspondyly</td>
<td>Normal, no extraskeletal manifestations</td>
<td>Autosomal dominant</td>
<td>4p</td>
<td>COMP</td>
<td>Cartilage oligomeric matrix protein</td>
</tr>
</tbody>
</table>

### Table 2. Pseudoachondroplasia.

| Pseudoachondroplasia | Head and face normal, short trunk, short stature, hands and feet shorter than in real achondroplasia, legs bowed, waddling gait | Atlanto-axial instability, scoliosis, premature osteoarthritis especially of the hips | Odontoid hypoplasia, vertebral end-plate irregularity, coxa vara, deformity of the femoral head, short tubular bones are widened | Normal intelligence, neurological symptoms and signs due to atlanto-axial instability | Autosomal dominant | 4p | COMP | Cartilage oligomeric matrix protein |
### Table 3. Achondroplasia group.

<table>
<thead>
<tr>
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<th>Gene</th>
<th>Protein</th>
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</thead>
<tbody>
<tr>
<td>Classic achondroplasia</td>
<td>Large head, prominent forehead, depressed nasal bridge, dwarfism with short limbs, especially the proximal portions (rhizomelic micromelia), stubby, trident hands, increased lumbar lordosis, waddling gait, prominent buttocks</td>
<td>Genua vara, secondary osteoarthritis of the hip and knee, flexion contracture of the elbows, increased lumbar lordosis, dorsal kyphosis, narrow spinal canal, degenerative spinal changes</td>
<td>Rounded iliac wings, short femoral necks, genua vara, shortening of the tubular bones, shortening of the ribs, anterioposterior diameter of the chest decreased, constricted basocranium, small foramen magnum, vertebral bodies bullet-shaped and flattened, in childhood, posterior part concave, pedicles short</td>
<td>Normal intelligence, compression of spinal cord, brain stem roots and cauda equina, sleep apnoea, sudden death</td>
<td>Autosomal dominant</td>
<td>4p</td>
<td>FGFR3</td>
<td>FGFR2</td>
</tr>
<tr>
<td>Hypochondroplasia</td>
<td>Features of chondroplasia are mild, face is not characteristic, short stature, increased lumbar lordosis, bow legs, elbow contractures</td>
<td>Hip and elbow involvement, prominent ulnar styloid process, short increased lumbar lordosis, narrow spinal canal, degenerative spinal disease</td>
<td>Shortening of tubular bones, mild metaphyseal flaring, shortened iliac bones, flattened acetabular roof, broad femoral neck, platyspondyly, posterior part of the vertebral bodies concave, short pedicles</td>
<td>Normal intelligence, nerve root or cauda equina compression, spinal cord compression may occur</td>
<td>Autosomal dominant</td>
<td>4p</td>
<td>FGFR3</td>
<td>FGFR2</td>
</tr>
</tbody>
</table>

### Table 4. Spondyloepiphyseal dysplasia congenita group.

<table>
<thead>
<tr>
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<th>Gene</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spondyloepiphyseal dysplasia congenita</td>
<td>Flat face, cleft palate, short trunk stature, short neck, mild shortening of the limbs, pectus carinatum</td>
<td>Atlanto-axial instability, kyphoscoliosis, increased lumbar lordosis, joint contractures, genu varum or valgum, premature osteoarthritic of the hip and knee</td>
<td>Hypoplastic odontoid process, pear-shaped vertebrae, anterior wedging, shortening of the femoral neck, small femoral head below the trochanteric level</td>
<td>Normal intelligence, myopia, retinal detachment, spinal cord compression</td>
<td>Autosomal dominant</td>
<td>12q13.1–q13.3</td>
<td>Col2A1</td>
<td>Type II collagen</td>
</tr>
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</table>
Spondyloepiphyseal dysplasias

Spondyloepiphyseal dysplasias (SEDs) are chondrodysplasias with epiphyseal and also spinal involvement, resulting in a short trunk short stature. Most but not all are associated with COL2A1 gene mutations.

Spondyloepiphyseal dysplasia congenita. In spondyloepiphyseal dysplasia congenita, the disease is caused by specific mutations of the COL2A1 gene, altering the normal Gly X–Y triplet structure of the corresponding region of type II collagen.

The features of this disease are listed in Table 4. It is often associated with premature OA of the hips and knees. The coxa vara is striking, the femoral neck is wide, the greater trochanters ride high, and the small femoral heads are deformed. The genu valgum is marked. Premature OA of the knee also frequently develops.

Spondyloepiphyseal dysplasia tarda. Spondyloepiphyseal dysplasia tarda (SEDT) is a short trunk short stature disorder, usually more noticeable in adolescence, characterized by hump-shaped vertebrae and premature OA of the hip, the shoulder and rarely the knee and ankle.

This disorder is inherited as an X-linked condition, in both a dominant and a recessive manner. It is possible that the recessive form is associated with a defect in the gene at Xp22.2–22.1, but the SEDT gene has not yet been identified. A developmental disturbance of enchondral bone formation is reflected in the radiologically inapparent ring apophysis. The features of this disease are shown in Table 5.

The dense areas of the vertebral end-plates can at first glance be mistaken for the disc calcification seen in ochronosis, but differentiation is easy on closer examination. SED with progressive pseudo-rheumatoid arthropathy is discussed below in the section on diseases mimicking OA of the hand.

Chondrodysplasia punctata group

This group of chondrodysplasias is rather heterogeneous. The common characteristic of the group is the small focal calcification in articular and non-articular cartilage in infancy, with ichthyosis of the skin and cortical cataract. The rhisomelic type is lethal.

Conradi–Hünermann disease. This is a milder form: the patient may survive to adult life. Asymmetric limb shortening, epiphyseal alterations and kyphoscoliosis are common. Coxa vara and premature OA of the hip may develop. Figure 1 shows chondroplasia punctata of the pelvis and ankle in a child.

Conradi–Hünermann disease is inherited as an X-linked dominant trait. Mutations in the gene encoding 3-beta-hydroxysteroid-delta-8,-delta-7-isomerase have recently been identified as a cause of Conradi–Hünermann disease and mapped to chromosome Xp11.22–p11.23. Sterol-delta-8 isomerase (EBP) mutations were found in all the probands. The features of this disease are shown in Table 6.

Phenocopies. Very similar disorders – phenocopies – can be caused by environmental factors. Chondrodysplasia punctata, short stature epiphyseal dysplasia, is a feature of these phenocopies, but no skin and eye involvement occurs. Warfarin embryopathy is caused by the mother’s anticoagulant use during the first trimester of pregnancy. Chondrodysplasia punctata also occurs in the neonates of patients with maternal lupus erythematosus.
### Table 5. Spondyloepiphyseal dysplasia tarda.

<table>
<thead>
<tr>
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<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-linked spondyloepiphyseal dysplasia tarda</td>
<td>Normal head and face, short trunk stature, nearly normal length of limbs</td>
<td>Atlanto-axial instability, degenerative spinal disease, thoracic disc herniation, premature osteoarthritis of the hips</td>
<td>Deformed odontoid process, disc spaces of the lumbar spine wide anteriorly and narrow posteriorly, hump-shaped areas of dense bone on the central and posterior portions of the end-plate, mild flattening of the epiphyses, coxa vara</td>
<td>Normal intelligence, nerve root and spinal cord compression, Chiari malformations, tonsillar ectopia</td>
<td>X-linked</td>
<td>Xp22</td>
<td>SEDL</td>
<td></td>
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</table>

### Table 6. Chondrodysplasia punctata.

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>Conradi–Huënermann type</td>
<td>Prominent forehead, flattened bifid nasal tip, deep nasal bridge, squareness of hands, asymmetrical limb shortening with joint contractures, club feet</td>
<td>Asymmetrical contractures, genu valgum, dislocated hips, scoliosis, kyphoscoliosis</td>
<td>In childhood punctate calcification of unossified epiphyseal centres; later epiphyseal irregularity, flattening of the coronal clefts of the vertebral bodies</td>
<td>Mild retardation, ichthyosiform, blotchy, lyonized skin, asymmetrical cataract, microphthalmia, corneal clouding, alopecia, congenital cardiac malformation</td>
<td>X-linked</td>
<td>Xp11.22–p.11.23</td>
<td>EBP</td>
<td>sterol-delta 8-isomerase</td>
</tr>
</tbody>
</table>
Maternal alcoholism causing alcoholic embryopathy has also been reported, with most of the common features of hip joint dysplasia, although kyphosis and contractures also may occur.33

Kniest and Stickler dysplasia group

Stickler’s syndrome (arthro-ophthalmopathy). This is a chondroplasia characterized by special facial features, abnormalities of the vitreous gel architecture associated with high myopia, normal height, a slender, even marphanoïd, figure, enlarged joints with mild epiphyseal dysplasia causing premature OA, and a spinal disorder resembling Scheuermann’s disease.63

The majority of cases of Stickler’s syndrome with the type 1 vitreous phenotype have mutations in the COL2A1 gene. Those with the type 2, vitreous, phenotype possess mutations in COL11A1 or COL11A2, which cause a syndrome with the systemic features of Stickler’s syndrome but without ophthalmopathy.20 The features of Stickler’s and Kniest’s syndromes are shown in Table 7.

Kniest’s dysplasia, or Swiss cheese syndrome. Kniest’s dysplasia is characterized by a short trunk, short stature appearance, mid-face hypoplasia, severe myopia and hearing loss. Like Stickler’s syndrome, Kniest’s dysplasia is caused by mutations of the COL2A1 gene as well as of the COL11A1 gene.20 Small deletions in the type II collagen triple helix produce this kind of chondrodysplasia.64

Mucopolysaccharidoses

The so-called mucopolysaccharidoses constitute group 10 of the international classification of osteochondrodysplasias, under the name of dysostosis multiplex.13 The mucopolysaccharidoses are storage diseases caused by an inherited lack of various lysosomal enzymes.18 In this chapter, we will discuss only those mucopolysaccharidoses whose victims survive to adulthood, which do not cause severe mental retardation, and whose articular involvement can be of clinical importance. The features of these mucopolysaccharidoses are shown in Table 8.
<table>
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</tr>
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<tbody>
<tr>
<td>Kniest’s dysplasia, Swiss cheese syndrome</td>
<td>Flattened face, depressed nasal bridge, cleft palate, short trunk, prominent joints</td>
<td>Kyphoscoliosis, increased lordosis, peri-articular and osseous enlargement similar to Heberden’s and Bouchard’s nodes, hip contracture, club feet</td>
<td>Vertebral flattening, wedge-shaped vertebrae, end-plate irregularity, rounded iliac bones, coxa vara, flattened and irregular epiphyses, short tubular bones, peri-articular osseous enlargement, epiphyseal and metaphyseal flaring</td>
<td>Normal or decreased intelligence, myopia, retinal detachment, deafness, inguinal hernia</td>
<td>Autosomal dominant</td>
<td>12q13.1–q13.3</td>
<td>COL2A1</td>
<td>Type II collagen</td>
</tr>
<tr>
<td>Stickler’s syndrome (arthro-opthalmopathy)</td>
<td>Depressed nasal bridge, small mandible, underdeveloped anterior part of the maxilla, cleft palate, short trunk, short limbs but usually normal stature</td>
<td>Spinal disease resembling Scheuermann’s disease, enlarged joints with swelling, clinodactyly of the fifth finger, premature osteoarthritis</td>
<td>Vertebral changes resembling Scheuermann’s disease, hypoplastic ilial wings, coxa valga, accessory ossicles, epiphyseal flattening, joint space narrowing</td>
<td>Usually normal intelligence, severe myopia, retinal detachment, vitreoretinal degeneration, neurosensory hearing loss</td>
<td>Autosomal dominant</td>
<td>12q13.1–q13.3</td>
<td>COL2A1 COL11A1</td>
<td>Type II collagen</td>
</tr>
<tr>
<td>Designation or eponym</td>
<td>Head and face, stature and proportions</td>
<td>Joint and spinal involvement</td>
<td>Radiology</td>
<td>Mental status, extraskeletal manifestations</td>
<td>Laboratory</td>
<td>Inheritance</td>
<td>Chromosome</td>
<td>Gene</td>
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</tr>
<tr>
<td>MPS-I-S, Scheie’s synochromoe</td>
<td>Coarse facial features, broad mouth with downturned corners, short or normal stature</td>
<td>Joint contractures, carpal tunnel syndrome</td>
<td>Proximal tapering of metacarpal bones, proximal convergence of metacarpal axes, small, crowded carpal bones</td>
<td>Normal intelligence, corneal opacity, aortic valvular disease, sleep apnoe</td>
<td>Urinary dermatan and heparan sulfate ↑, metachromatic inclusions in lymphocytes: Gasser cells</td>
<td>AR</td>
<td>4q16,3</td>
<td>IDA</td>
</tr>
<tr>
<td>MPS-II, Hunter’s syndrome</td>
<td>Coarse facial features, broad nasal bridge, widely spaced, prominent eyes, short stature</td>
<td>Claw hands, joint contractures</td>
<td>Hypoplasia of acetabular and supraacetabular portion of iliac bones oxva valga, ovoid vertebral bodies, OA of the hip</td>
<td>Normal intelligence, or a mild retardation, increased intracranial pressure may occur, no corneal opacity, deafness, organomegaly, cardiac defects</td>
<td>Urinary dermatan and heparan sulfate ↑, Gasser cells</td>
<td>XLR</td>
<td>Xq27.3-q28</td>
<td>IDS</td>
</tr>
<tr>
<td>MPS IV, Morquio’s disease</td>
<td>Lower part of the face is prominent and accentuated, short trunk, short stature, prominent joints, sternal protrusion, knock-knees, waddling gait</td>
<td>Atlanto-axial instability, thoracic kyphosis, early OA, knock-knees</td>
<td>Hypoplastic odontoid process, platyspondyly, oxva valga, acetabular hypoplasia, conically shaped bases of II–Vth metacarpals</td>
<td>Normal intelligence, fine corneal opacities, impaired hearing, spinal cord compression. Hepatomegaly, enamel hypoplasia</td>
<td>Urinary chondroitin sulfate, keratan sulfate ↑, Gasser cells, Buhot cells: plasma cells with metachromatic inclusions</td>
<td>AR</td>
<td>Type A 16q23,4,3 Type B 3p21,2-p14,2</td>
<td>GHL N</td>
</tr>
<tr>
<td>MPS-VI, Maroteaux-Lamy disease</td>
<td>Gargoilic face Short trunk, short stature, macrocephaly</td>
<td>Joint contractures, atlantoaxial instability, early OA of the hip</td>
<td>Hypoplastic odontoid process biconvex vertebral ilial and acetabular hypoplasia, shortening and widening of metacarpal bones</td>
<td>Normal intelligence, corneal opacities, spinal cord compression, vertebral insufficiency</td>
<td>Urinary dermatan-sulfate ↑, coarse, dense granules in white blood cells; Alder’s anomaly</td>
<td>AR</td>
<td>Sq1 3,3</td>
<td>ARS B</td>
</tr>
</tbody>
</table>
Aetiology. The mucopolysaccharidoses are one of the most thoroughly studied groups of osteochondrodysplasias; the genes at fault are well known. The lack of enzyme results in the storage of mucopolysaccharides in the cornea, central nervous system, heart, liver and spleen, as well as in the bones, joints and ligaments. The involvement of osteoarticular structures leads to multiple joint contractures, carpal tunnel syndrome, atlanto-axial instability and premature OA, while the deposition of mucopolysaccharides in other organs results in, for example, organomegaly, mental retardation, corneal opacities, hearing loss and cardiac disease.

Animal models closely resembling the human disorder have been developed, and methods of gene treatment using different viruses as carriers for replacement of the deficient enzyme are being studied.

Treatment. The gene treatment technique has now been developed to such a level that human clinical trials can be started. In a feline model of type VI mucopolysaccharidosis, intravenous recombinant human N-acetylgalactosamine-B-sulphatase was used, the kittens being treated from birth. A near-normalization of lysosomal storage was observed in almost all of the organs, but with the exception of cartilage and the cornea. Spinal compression and other skeletal involvements were reduced.

The treatment currently available is bone marrow transplantation. The mechanism of improvement achieved by bone marrow transplantation is not fully understood, a number of methods having been suggested. The biochemical correction is, however, certainly reflected in the reduced concentration of storage product in the blood, urine and tissues, and the concentration of the deficient enzyme considerably increased. The transplant-related mortality, however, was high (10%) in HLA-identical sibling donors and even higher (20–25%) when mismatched tissue was used. The survival rate increased by 5 years in Hurler’s syndrome. The cardiac, mental and neurological disease, as well as the obstructive sleep apnoea, significantly improved, but the dysostosis multiplex progressed or did not improve, even though the joint contractures lessened.

In Maroteaux-Lamy syndrome (MPS-VI), only a few patients have been treated by bone marrow transplantation. In the published cases, there was no mortality, although graft-versus-host disease of varying severity developed in several instances. The cardiac disease and obstructive sleep apnoea considerably improved. The facial features, the mental status and the joint contractures, but not the skeletal status, also improved. Shelf acetabuloplasty and varus osteotomy were performed in two cases to relieve hip stiffness, the patients remaining active and mobile. The carpal tunnel syndrome common in children with mucopolysaccharidosis can be effectively treated by surgery and physiotherapy.

Metaphyseal dysplasias

The metaphyseal dysplasias are characterized by a short limb, short stature appearance with bowed forearms and legs, and small hands and feet when the metaphyses of the small tubular bones are also affected.

Aetiology. The metaphyseal dysplasia group is probably heterogeneous regarding aetiology. In Jansen-type metaphyseal dysplasia, mutations of the PTH/PTHrP gene are found, in adenosine deaminase (ADA) deficiency mutations of ADA gene (chromosome 20q13.11) are suspected.
Schmid-type metaphyseal dysplasia is an autosomal dominant disorder with metaphyseal flaring, especially of the femur and tibiae and anterior part of the ribs. As a rule, coxa vara develops, causing later premature OA of the hip; OA of the knee also frequently develops. Mutations of the collagen X (COL10A1) gene are the cause of Schmid-type metaphyseal dysplasia. It is also well known that type X collagen is expressed in the hypertrophic region of the growth plate cartilage. The mutations causing the disease appear within the carboxy-terminal globular domain (NC1) of type X collagen. Evidence for a co-assembly of the mutant and wild-type protein containing and binding to molecular chaperones has recently been presented.

Cartilage–hair hypoplasia (CHH) syndrome (or McKusick-type metaphyseal dysplasia) was originally described in the Amish in the USA by McKusick; it is also common in a small area of Western Finland. CHH syndrome is inherited in an autosomal recessive manner and is characterized by metaphyseal chondrodysplasia, hypoplastic hair growth, sparse hair and combined immune deficiency resulting in recurring respiratory infections; as such, it is often fatal during the first year of life. Immune deficiency is characterized by a lower number of CD4+ cells and a lower CD4:CD8 ratio, a higher than normal number of NK cells, and a subnormal response to lymphocyte stimulation. The currently used parameters of cellular immunity poorly predict the outcome of the disease in the individual patient. Bone marrow transplantation fully corrects the immune deficiency but not the chondrodysplasia.

Adenosine deaminase deficiency is an autosomal recessive disorder characterized by combined immune deficiency, mild metaphyseal dysplasia, dense metaphyseal lines (growth arrest lines), broad, squared ilia, cupping and flaring of the anterior ribs, and flattened vertebrae. The immune deficiency is characterized by lymphopenia, an absent response to mitogens, a deficiency of mature lymphocyte surface markers and a lack of erythrocyte adenosine deaminase. Recurrent life-threatening infections are common. Bone marrow transplantation and polyethylene (PEG)-conjugated adenosine deaminase injections cure or incompletely correct the immune deficiency, also reversing the osteochondrodysplasia.

Familial hypophosphataemic rickets and osteomalacia

Familial rickets and osteomalacia is a hereditary, vitamin-D resistant metabolic disease characterized by renal phosphate wasting and various musculoskeletal symptoms – myopathy, pseudofractures, diffuse skeletal calcification, hyperostosis (DISH syndrome) and secondary OA of the hip and knee. The skeletal signs of hypophosphataemic rickets were recently discovered in an 11 000-year-old paleopathological case. Inheritance follows the X-linked, autosomal dominant pattern: large kindreds of childhood or adolescent (rickets) and adult-onset (osteomalacia) cases have been described in the past two decades. The gene seems to be linked to chromosome 12p13.

In rheumatology practice, the adult-onset form of osteomalacia may present a differential diagnostic problem. The leading clinical feature is the progressive myopathy, with a characteristic waddling gait caused by weakness of the gluteus medius muscle. Pseudofractures of the ribs and the long bones sometimes lead to real fractures, for example hip fracture, later causing secondary OA of the hips and knees. An X-ray of one of our patients with a pseudofracture and secondary OA of the hip is shown in Figure 2.

High-dose phosphate and calcitriol treatment can slow or halt the progression of both renal and musculoskeletal symptoms but is unable to reverse the whole pathological process.
Hereditary hypophosphatasia

The term ‘hereditary hypophosphatasia’ represents a group of heterogeneous clinical syndromes with at least two different inheritance patterns and various enzyme abnormalities and gene localizations. The common feature of these syndromes is the missing or decreased activity of one or more of the alkaline phosphatase isoenzymes, causing an abnormal mineralization of osteoid tissue and epiphyseal cartilage. Prenatal diagnostics is based on chorionic villus biopsy, which can prove normal or diseased alkaline phosphatase alleles.80

Clinically, the condition presents with rickets- or osteomalacia-like lesions, including multiplex bone fractures and secondary OA of the affected joints. Symptoms depend on the age of onset, perinatal, infantile and childhood forms being the most severe, sometimes with no signs of any mineralized bone tissue. Late adolescent or adult-onset forms are usually milder, with pathological fractures and secondary OA.82

Unlike those with rickets or osteomalacia, hereditary hypophosphatasia patients are usually resistant to treatment, including high doses of the active metabolites of vitamin D. Symptomatic therapy, such as dietary calcium restriction and orthopaedic rehabilitation of the fractures, is usually recommended.80

Polyarticular diseases affecting the hands and mimicking early OA

Disorders of different origins can be included in this group, but we will discuss here only diseases developing in childhood and early adolescence, and exclude congenital diseases, such as arthrogryposis multiplex congenita and congenital contractual arachnodactyly; mucopolysaccharidoses associated with claw-hands have been discussed above. Similarly,

Figure 2. Adult-onset familial vitamin-D resistant hypophosphataemic osteomalacia. X-rays of a fracture of the left hip (A) and pseudofractures of the ribs (B).
inflammatory disorders such as velocardiofacial syndrome, a variant of di Giorgi syndrome, and trisomy-associated arthritides will not be discussed.

The conditions that will be described are Thiemann’s disease, camptodactyly–arthropathy–coxa vara–pericarditis syndrome (CACPS) and progressive pseudo-rheumatoid dysplasia. These conditions also may mimic JCA, although no inflammatory feature is present in any of them.

**Thiemann’s disease**

Thiemann’s disease is an idiopathic avascular necrosis of the epiphyseal parts of the proximal and middle phalanges, the articular bones of the proximal interphalangeal joints. This is, to our knowledge, the only hereditary avascular bone necrosis. Its inheritance is autosomal dominant, with strong penetration, and it affects mostly males. The disease may be apparent as early as 4 years of age, but in some does not appear until as late as the age of 40. Enlargement of the proximal interphalangeal joints occurs first, followed by flexion contractures. The disease usually starts in the middle finger, followed by the second and the fourth fingers, the fifth finger and thumb often being spared. Shortening of the second and third phalanges often develops. In the early phases, radiographs show flattening and irregular fragmentation of the epiphyses, the epiphyses later disappearing, the bases of the phalanges becoming thickened and the joint spaces narrowed. The toes and the metacarpophalangeal joints are very rarely affected.

The disorder is usually painless, causing little disability. The patient described by Molloy and Hamilton, however, had extreme joint tenderness. Handa et al’s patient, in spite of lacking the physical and laboratory signs of inflammation and tenderness, was misdiagnosed as having JCA and was treated with low-dose prednisone and diclofenac without any effect before the correct diagnosis was reached.

**Camptodactyly–arthropathy–coxa vara–pericarditis syndrome (CA CPS)**

CACPS is characterized by congenital camptodactyly and childhood-onset non-inflammatory arthropathy, bilateral coxa vara deformity developing in later childhood, as well as, in some cases, the symptoms and signs of pericarditis.

**Aetiology.** CACPS is an autosomal recessive disease, the gene being located on the first human chromosome (1q25–q31), the location of the involved gene has not yet been determined.

**Clinical features.** Arthropathy affecting the large joints (wrists, elbows, knees, hips and ankles) develops in childhood, with synovial hyperplasia but no evidence of concurrent inflammation. Histologically, villous hypertrophy with necrotic villi, multinucleated giant cells and a lack of inflammatory cells or vasculitis can be seen. The pericarditis — sometimes requiring puncture and/or operation, sometimes spontaneously healing — is also non-inflammatory.

Fibrosis occurs also in the pericardium and the tendon sheets because of regular dysfunction in the proliferation of synovial and other cells. Coxa vara usually develops later in childhood, its pathogenesis being unknown. In one of Bahabri et al’s cases, coxa magna with cystic lesions developed. Tenolysis and tenosynovectomy have been performed on some patients.
Progressive pseudorheumatoid dysplasia

Progressive pseudorheumatoid dysplasia is characterized by SED with platyspondyly and progressive, but non-inflammatory, arthropathy mimicking JCA, RA and adulthood polyarticular OA.3,87

Aetiology. The disease is heritable as an autosomal recessive trait. Although the gene causing the disease has not yet been determined, it is certainly placed on the longer arm of human chromosome 6 (6q21), the chromosome on which the \textit{COL10A1} gene is located. \textit{COL10A1} cannot be totally excluded as the gene causing the disease. Five genes encoding collagen and one encoding a specific procollagen-processing enzyme are good candidates for the progressive pseudorheumatoid dysplasia gene.88,89

Clinical features. The clinical symptoms and signs of the disease appear in early childhood. Progressive enlargement of the epiphyses of the elbows, hips, knees and interphalangeal joints develops, causing joint enlargement and deformity, with progressively increasing flexion contractures. The condition mimics RA, but no physical or laboratory signs of inflammation develop. Synovial biopsy shows a normal synovial membrane.

Short trunk dwarfism usually develops, although cases with normal stature have also been reported. Shortness of the trunk is the result of platyspondyly, sometimes with kyphosis or kyphoscoliosis. Enlargement of the metaphyses and epiphyses, joint space narrowing and premature OA, especially of the hips, are characteristic, along with a broad femoral neck and coxa vara. Genu valgum also frequently occurs. Disability is caused by increasing flexion contractures, especially of the hip and knee, requiring soft tissue release, osteotomy and joint replacement. The patient complains of mild pain and stiffness, but anti-rheumatic treatment is ineffective.3,87,90 Mental retardation and features such as dysmorphism and corneal capacity are not seen in this disease.

In the differential diagnosis, other non-inflammatory arthropathies affecting the finger joints should be considered, for example diabetic cheiroarthropathy, frost-bite arthropathy, haemochromatosis, mucopolysaccharidoses and congenital contractural arachnodactyly.84

Other dysostoses

Of the numerous dysostoses affecting only a single bone, only nail–patella syndrome (NPS) is discussed here as an example, partly because of its relative infrequency and partly because the syndrome is associated with extraskeletal pathology.

Nail–patella syndrome

NPS is a rare disorder of autosomal dominant inheritance.91 Its prevalence in the population is 1 in 50,000 live births. The syndrome is characterized by dysplasia and hypoplasia of the nails, aplasia or dysplasia of the patella (see Figure 3), decreased mobility of the elbow, iliac and scapular horns, and rarely nephropathy (membranous glomerulonephritis) and open-angle glaucoma.

The condition was first described in 1897 by Little, and later by Turner. The genetic linkage between NPS and the ABO blood group was reported in 1955.91 This rare familial disorder was initially mapped to the adenylate kinase loci on human
chromosome 9q34. The syndrome seems to appear as a result of haploinsufficiency and mutations in the LIM-homeodomain gene \textit{LMX1B}.\textsuperscript{92} An isolated patella aplasia–hypoplasia syndrome was recently described in an extended Venezuelan family, the NPS gene being localized between D17S787 and D17S604 within the region of 12cM on chromosome 17q22.\textsuperscript{93}

The importance of the NPS for rheumatologists is twofold. First is the tendency towards premature OA, caused biomechanically by the absent or missing patella. This secondary OA is usually mild, and its progression can be prevented by non-

\textbf{Figure 3.} Nail–patella syndrome: note the dystrophic nails (A) and the hypoplastic patellae with bilateral genu valgum (B).
pharmacological methods, such as quadriceps strengthening exercises. Second, by the recognition of musculoskeletal signs may lead to the identification and treatment of important extraskeletal manifestations such as renal and eye disease.

INBORN ERRORS OF METABOLISM CAUSING PREMATURE OA

The term and concept of ‘inborn error of metabolism’ were first described and coined by Sir Archibald Garrod, who noted the autosomal recessive trait of alkaptonuria and ochronosis, and proved that Mendelian laws are applicable to humans.94,95

A number of inborn errors of metabolism are also associated with cartilage damage. Their main feature is that, unlike for example the heritable osteochondrodysplasias, the development of the joints and their anatomical structure is initially normal. The mechanism of cartilage damage is best known in ochronosis and haemochromatosis, but is not quite clear in Wilson’s disease. Although the specific inborn error of metabolism causing familial chondrocalcinosis is unknown, we will also discuss this disorder here.

Ochronosis

Aetiology and pathogenesis. Half a century later than Garrod noted the method of inheritance of ochronosis, La Du et al proved the aetiological factor underlying the condition to be a deficiency of homogentisic 1,2-dioxygenase.96 The human HGO gene, assigned to chromosome 3q21–q23, has recently been cloned97,98 and characterized, and a number of mutations responsible for the lack of enzyme activity described.99,100

In humans, phenylalanine and tyrosine metabolize via hydroxyphenylpyruvic acid and homogentisic acid (HGA) to maleil-acetoacetic acid. In the absence of the effect of the HGO gene, homogentisic acid is the end-product, being excreted in large amounts (up to 15 g) in the urine, depending on the phenylalanine and tyrosine intake of the patient. The pathognomic black discoloration of the urine that appears when it is oxidised or alkalinized gives the condition its name of alkaptonuria. HGA also oxidizes to benzoquinone-acetic acid, which polymerizes to a melanin-like pigment. The pigment is macroscopically bluish-black, but microscopically it appears brownish-yellow or ochre, providing the designation ‘ochronosis’ as given by Wirchow.101 The deposition of the pigment in the joint tissues causes symptoms and signs, usually in the fourth decade of life. Other external quinones, such as skin-bleaching creams, may cause similar discoloration and pigmentation.102 The polymerized pigment binds to the collagen fibres, causing a loss of striation, swelling and fracture.103

Epidemiology. The prevalence of alkaptonuria is approximately 1 in 250 000, although it is more frequent in some countries, such as Slovakia104 and the Dominican Republic.105 It has also been recognized in Egyptian mummies.106

Clinical features. There are excellent reviews on alkaptonuria and ochronosis: O’Brien et al107 have provided a review of world literature published between 1584 and 1962 on this topic and La Du has recently published an outstanding overview of the subject.108

The typical sites for detecting ochronotic pigmentation are the pinna of the ear and the sclera, where it characteristically deposits at the insertion of the ocular muscles. The
pigmentation of the sclera is usually not bluish-black but brownish. Discolouration may appear over the nose, the axillae, the groin and all those sites where the affected cartilage and/or tendon sheets are superficial enough to be visible through the skin. Other sites of the extra-articular deposition of ochronotic pigment are shown in Table 9.

The visible pigment deposits, especially in the sclera, usually precede the occurrence of musculoskeletal symptoms and signs, the diagnosis therefore often being made by an ophthalmologist. The blue-black pigmentation may mimic melanoma of the choroid.\textsuperscript{109}

Tendons and tendon sheets are frequently affected, this being a characteristic feature that differentiates ochronosis from polyarticular OA. Tendon calcification and rupture of the ochronotic Achilles tendon have been reported.\textsuperscript{110} The severe destructive joint disease of the hips and the knees often requires surgery, including joint replacement.\textsuperscript{100}

The differentiation of this condition from ankylosing spondylitis is not very difficult, calcification of the discs not being a feature of ankylosing spondylitis, and sacroilitis not being a feature of ochronotic spondylopathy. Fusion of the sacroiliac joints rarely occurs.\textsuperscript{100} The differentiation of peripheral arthropathy from other kinds of OA is, however, more difficult. The characteristic pigmentation found in the sclera and the ear, and the characteristic spondylopathy, provide clues to the proper diagnosis. Finding the ochronotic pigment in the synovial fluid or in the synovial fluid cells can provide diagnostic proof.\textsuperscript{111,112} The musculo-skeletal manifestations of ochronosis are shown in Table 10.

Patients with ochronosis often have some cardiac involvement, manifesting as murmurs, valve involvement or aortic stenosis.\textsuperscript{100}

\textit{Treatment.} There is currently no method for correcting the underlying pathology or substituting the missing enzyme. A reduction in intake of phenylalanine and tyrosine is in theory beneficial but in practical terms cannot be practised for long. Ascorbic acid inhibits the oxidation of HGA to ochronotic pigment in vitro, but the efficacy of long-term ascorbinic acid administration has been never proved. The triketone herbicide NTBC, an inhibitor of 4-hydroxyphenylpyruvate dioxygenase, the enzyme producing HGA, has recently been suggested as a possible agent for treatment.\textsuperscript{113}

One of the promises of the near future is enzyme replacement using the recombinant production of HGO.\textsuperscript{114} Animal models for alkaptonuria – aku mice – are available for animal trials.\textsuperscript{115,116}

\begin{table}[h]
\centering
\begin{tabular}{|l|}
\hline
Sclerae \\
Sweat glands \\
Non-articular cartilage (larynx, bronchial cartilage) \\
Ligaments, tendons and fascia \\
Heart valves and rings \\
Endo- and pericardium \\
Arteries and arterioles \\
Macrophages \\
Kidney, also producing renal stones \\
Prostate, also producing calculi \\
Langerhans islet cells \\
Adrenal glands \\
\hline
\end{tabular}
\caption{Sites of extra-articular deposition of ochronotic pigment.}
\end{table}
Wilson’s disease

Wilson’s disease is an inborn error of copper metabolism characterized by the deposition of copper in the liver, brain and other organs, which results in hepatic, neurological and psychiatric disease, as well as causing haematological and osteo-articular symptoms and signs.5

Prevalence. The genetic frequency of Wilson’s disease has been estimated to be 1 in 200 and the prevalence of the disease 1 in 30 000. the clinical features may appear anywhere between the ages of 3 and 50.5

Aetiology. Wilson’s disease is an autosomal recessive disorder, the WD gene being located on chromosome 13 (13q1–q21). Mutations of the gene ATP7B, a copper-transporting adenosine triphosphatase, result in the impaired hepatic excretion of copper and an impaired incorporation of copper into coeruleoplasmin. Cloning and characterization of the promoter region of the Wilson’s disease gene have recently been undertaken.117

Pathogenetics and pathology. In Wilson’s disease, there is a deficiency or absence of coeruleoplasmin, the blue alpha globulin with a molecular weight of 131 kDa that binds six atoms of copper as both cupric and cuprous ions. The normal plasma concentration of coeruleoplasmin is 200–400 mg/l. The other copper-carrying proteins are found in

<table>
<thead>
<tr>
<th>Table 10. Musculoskeletal manifestations of ochronosis.</th>
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<tbody>
<tr>
<td><strong>Spondylopathy</strong></td>
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<tr>
<td>Disc space narrowing</td>
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<tr>
<td>Calcification and ossification of discs and ligaments</td>
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<tr>
<td>Vacuum sign in discs</td>
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<tr>
<td>Wafer-like calcification of intervertebral discs</td>
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<tr>
<td>Degenerative inflammatory changes in the sacroiliac joint</td>
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<tr>
<td>Clinically:</td>
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<tr>
<td>Stiffness of the spine</td>
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<tr>
<td>Lack of lumbar lordosis</td>
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<tr>
<td>Moderately increased kyphosis</td>
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<tr>
<td>Mild or moderate pain</td>
</tr>
<tr>
<td><strong>Peripheral arthropathy</strong></td>
</tr>
<tr>
<td>Secondary osteoarthritis affecting mostly the large joints</td>
</tr>
<tr>
<td>Specific signs:</td>
</tr>
<tr>
<td>Bluish, darkish synovial fluid</td>
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<tr>
<td>Ground pepper-like appearance of synovial fluid due to ochronotic debris</td>
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<tr>
<td>Intracellular pigment inclusions in synovial macrophages</td>
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<tr>
<td>Fragments of ochronotic pigmented cartilage, embedded in synovial tissue in biopsy specimen</td>
</tr>
<tr>
<td>Ochronotic deposition in tendons and tendon sheets, causing tendon calcification and rupture</td>
</tr>
<tr>
<td>Differentiating features from other kinds of osteoarthritis:</td>
</tr>
<tr>
<td>Fragmentation of the cartilage</td>
</tr>
<tr>
<td>Loose bodies</td>
</tr>
<tr>
<td>Osteochondromatosis</td>
</tr>
<tr>
<td>Joint locking</td>
</tr>
<tr>
<td>Chondrocalcinosis</td>
</tr>
<tr>
<td>Osteophyte formation minimal or moderate</td>
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</tbody>
</table>

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normal concentrations, but only a small percentage of copper is bound to these proteins or exists unbound in the plasma, most of the copper normally being bound to ceruloplasmin. The normal concentration of copper is between 15.7 and 23 mmol/l. The error in copper metabolism results in the storage of copper in the liver. The normal copper concentration in the liver is below 50 mg/g dry weight, while in Wilson’s disease it is over 150 mg/g dry weight and can be as high as 3000 mg/g dry weight.

The copper overloading of the hepatocytes is associated with structural and functional damage to the liver, but this is very often asymptomatic. The necrosis of hepatocytes caused by a copper overload may appear any time from the first to the fifth decade of life. In most cases, the hepatic damage is not fatal, but the release of copper from the damaged hepatocytes may cause copper-induced haemolysis. In other cases, the released copper does not cause haemolysis but enters the plasma and is excreted in the urine. (The normal urinary copper output is less than 0.6 mmol per 24 hours.) Even the increased urinary output of copper is not able to maintain the copper balance, the free plasma copper diffusing through the blood–brain barrier and being deposited in the basal ganglia, causing severe neurological and psychiatric symptoms and signs, such as ataxia, tremor, disdiadochokinesis, parkinsonism, chorea and dystonia. With different kinds of positron emission tomography and single photon emission computed tomography, a reduced striatal and cerebral cortical glucose uptake, as well as reduced pre-synaptic and post-synaptic striatal dopamine receptor binding, has been demonstrated.

**Diagnosis and clinical features of non-osteoarticular disease.** The Kayser–Fleischer ring, a greenish-brown discolouration of the outer margin of the cornea caused by copper deposition, is an early and pathognomonic sign, although in the large series (51 patients) of Stremmel et al, it was seen only in 67% of patients. The abdominal symptoms and signs of the disease are abdominal pain and hepat- and/or splenomegaly. Rapid liver damage may occur, causing death within a week of the appearance of the first symptoms. Cirrhosis develops in 10–14% of patients. Neurological signs develop in 40–50% of cases, tremor, dysarthria and an ataxic gait being the most common features. Thrombocytopenia appears in 10%. The diagnosis can be made even in asymptomatic patients when the family history suggests the possibility of the disease. A ceruloplasmin serum level of less than 200 mg/l, a serum copper output less than 12.6 mmol/h and a urinary copper output of over 1.6 mmol per 24 hours, increasing to above 16 mmol per 24 hours after d-penicillamine stimulation, are suggestive of Wilson’s disease. The diagnosis can be confirmed by the presence of the Kayser–Fleischer ring or by liver biopsy; in the case of Wilson’s disease the liver will contain more than 3.9 mmol/g dry weight of copper.

**Osteoarticular disease.** The symptoms of osteoarticular disease associated with Wilson’s disease include:

1. premature OA, affecting mostly the large joints such as the knees, hips and shoulders, and the spine;
2. chondrocalcinosis;
3. chondromalacia patellae;
4. osteoporosis, sometimes with fractures;
5. osteomalacia;
6. resorption of the lamina dura and reticular or cystic bone alterations resembling those of hyperparathyroidism.
In otherwise mild or asymptomatic cases, articular pain and stiffness may be the first, presenting symptoms, only a thorough family history revealing the cause of the complaints. Articular disease is usually polyarticular, involving the large joints, especially the knees and shoulders. Hand involvement is not frequent, but chondrocalcinosis of the triangular disc of the wrist, angulation of the metacarpal bones and swelling of the metacarpophalangeal joints have been reported.

The radiological features of premature OA associated with Wilson’s disease are marginal bone fragments, loose bodies, calcification of the joint capsule or tendon.

Figure 4. Ochronosis: X-rays of the pelvis (A) and spine (B). Note the sacroiliac involvement, the sclerotic surfaces of the pubic symphysis and the artheropathy of the ischial tuberosity (A) and the characteristic water-like calcifications of the lumbar discs (B).
insertion and squaring of metacarpal heads. Out of the 22 patients described by Menerey et al\textsuperscript{121} with osteoarticular Wilson’s disease, three had radiological evidence of chondrocalcinosis. In four patients, arthroscopy was performed, but none of them demonstrated radiological chondrocalcinosis. In none of these cases could calcium pyrophosphate dihydrate (CPPD) or hydroxyapatite crystals be detected.\textsuperscript{121} Light microscopy showed slight proliferation of the synovial lining cells with increased villi or was unremarkable. Electron microscopy showed some variation of the collagen fibres and dark, scattered, degenerated chondrocytes. Synovial lining cell mitochondria were unusually dark and had widely dilated cisternae, with prominent mast cells.\textsuperscript{121} By energy dispersive elemental analysis of cartilage samples from two patients, the same authors showed peaks for copper and sulphur diffusely throughout the cartilage.\textsuperscript{6} 

The pathomechanism of the development of mild premature OA in Wilson’s disease is still unclear, but copper deposition in articular cartilage might play a part.

\textbf{Treatment.} Before the introduction of d-penicillamine treatment by Walshe in 1956, most patients died before the age of 30.\textsuperscript{122} d-Penicillamine has dramatically changed the course of the disease, although severe side-effects occur and also unresponsive patients may be encountered. Over the past 20 years, trientine (triethylene tetramine dihydrochloride) has been introduced as a chelating agent. This compound causes fewer side-effect but also chelates other trace elements, such as zinc. The cupriuretic effect of trientine is similar to that of d-penicillamine, the dose used being 1–2 g/day.\textsuperscript{123} Zinc, and recently tetrathiomolybdate, has been used for blocking the reabsorption of copper secreted endogenously in the alimentary tract. Brewer et al have published a follow-up study of 141 patients treated with long-term zinc monotherapy, with good results.\textsuperscript{124}

Chelation and reabsorption-blocking treatment dramatically changed the course of the disease. Out of 51 patients studied by Stremmel et al\textsuperscript{5}, only two died, as a result of fulminant hepatitis at a time when hepatic transplantation was not available. In two other patients, however, with end-stage liver disease, liver transplantation was performed with longlasting success: their copper metabolism normalized, and no copper-reducing treatment was required. The metabolic defect was seemingly resolved by the transplantation. Poorer results were published by Walshe and Yealland\textsuperscript{122}: out of their 137 patients, 20 died, 11 of whom were considered to have been adequately treated, with a satisfactory response regarding cupriuresis. Regarding brain disease, positron emission scan imaging is also used for measuring the effect of treatment on the glucose metabolism of the brain.\textsuperscript{119}

The best results can be achieved by the early treatment of pre-symptomatic patients. The pre-clinical diagnosis of this inborn error of copper metabolism is therefore very important; for this reason, screening with DNA probes may be used to detect homozygous patients in infancy.\textsuperscript{5} Early preventive treatment will hopefully entirely prevent the hepatic and neurological disorder as well as the premature OA.

\textit{Familial chondrocalcinosis} 

Familial articular chondrocalcinosis was first described in an ethnic Hungarian kindred in Slovakia.\textsuperscript{125} Although sporadic cases have been reported from all parts of the world, its prevalence seems to be highest in Spain.\textsuperscript{126} Two different phenotypes have so far been reported. In about one-third of the families, an early-onset, polyarticular-type involvement can be observed, with acute pseudogout attacks in the younger generations and severe destructive arthropathy in
the older members. The majority of the families present with a late-onset, oligo-articular CPPD deposition disease, which is clinically indistinguishable from that of the sporadic cases.\textsuperscript{127,128} The main difference between the two groups lies in the distribution of the articular involvement and the higher frequency of spinal symptoms, such as meningism, caused by intervertebral calcification in the cervical region.\textsuperscript{127}

Clinical and genetic studies have proved that familial chondrocalcinosis is an autosomal dominant entity with variable transmission penetrance, linked to the 5p15 region of chromosome 5.\textsuperscript{128,129} In addition, hypokalaemia and/or hypomagnesaemia seem to be an important pathogenetic factor, as shown in a common familial case of Bartter syndrome and hereditary chondrocalcinosis.\textsuperscript{130}

The significance of this syndrome for practical rheumatology is that patients with the polyarticular, premature-onset form of the disease can develop early and progressive secondary OA of the wrists, elbows, knees and hips, while patients with the mono- or oligoarticular pattern are slowly progressing, elderly patients, whose treatment is similar to that of primary OA of the hip and knee.

**SUMMARY AND CONCLUSIONS**

The genetic mapping of hereditable osteochondrodysplasias is progressing rapidly. There is evidence that mutations of collagen-encoding genes cause a number of these diseases: \textit{COL2A1} mutations causing some SEDs, Kniest dysplasia and Stickler’s syndrome; \textit{COL10A1} gene mutations causing Schmid-type metaphyseal dysplasia; and \textit{COL11A1} mutations causing type II Stickler’s syndrome. Mutations of the \textit{COMP} gene cause multiple epiphyseal dysplasia and pseudochondroplasia. Conradi–Hünermann-type chondrodysplasia punctata is caused by mutations of the \textit{EBM} gene. Chondrodysplasia punctata resulting from anticoagulant treatment during pregnancy, maternal lupus and maternal alcoholism is also well described. All these disorders may cause premature OA, especially of the hip and knee. In some diseases, such as Jansen-type metaphyseal dysplasia or pseudohyperparathyroidism, mutations of the \textit{PTH}/\textit{PTHrP} and G-protein genes may also play a role.

Achondroplasia and hypochondroplasia, the most common forms of osteochondrodysplasia, are caused by different mutations of the \textit{FGFR3} gene. The large joints of these patients, especially the knees and elbows, are deformed, with flexion contracture or hypermobility mimicking OA, but real OA rarely develops.

The molecular genetics of the mucopolysaccharidoses is well described. Those surviving to adulthood may develop joint contractures and may have a clinical picture resembling that of OA.

The immuno-osseous dysplasias, such as cartilage – hair syndrome and adenosine deaminase deficiency, are characterized by combined immune deficiency, resulting in recurrent respiratory infections.

Hereditable chondrodysplasias affecting the hands – pseudorheumatoid dysplasia CACPS and Thiemann’s disease – resemble not only polyarticular OA but also JCA and RA, resulting in unnecessary treatment.

In a number of these diseases, prenatal genetic and/or imaging diagnosis is available. A correct and early diagnosis, including that of the mild or incomplete forms, is important. Genetic and occupational counselling are possible, and other changes such as atlanto-axial instability, a narrow spinal canal and alterations to the internal organs, can be detected.
Bone marrow transplantation is now an effective treatment in the mucopolysaccharidoses and immuno-osseous dysplasias. Enzyme replacement therapy is already being used in treatment of adenosine deaminase deficiency and is a possibility for the treatment of mucopolysaccharidoses. Gene treatment for mucopolysaccharidoses is undergoing clinical trials and will probably also become available for other disorders. The genetic and molecular background of inborn errors of metabolism such as alkaptonuria, ochronosis and Wilson’s disease is now also well described.

Copper chelation and absorption inhibition treatments (d-penicillamine, trietine and zinc sulphate) are effective in preventing and treating the manifestations of Wilson’s disease.

HGA oxidase replacement therapy may prevent ochronosis and may soon become available.

Familial chondrocalcinosis may also cause premature OA.

### Practice points
- Remember heritable osteochondrodysplasias when seeing children or young adults with non-inflammatory small or large joint deformities and contractures, especially when these are associated with a disproportionately short stature.
- Think of alkaptonuria, Wilson’s disease or familial chondrocalcinosis when faced with a patient with premature OA even in the absence of other characteristic symptoms and signs.
- Remember that most of these conditions can have severe and often life-threatening complications, such as atlanto-axial instability, fulminant hepatic failure and cardiac disease.
- A proper diagnosis is of practical importance with respect to genetic and occupational counselling.
- In some cases, effective treatment is available, such as copper chelation and absorption treatment in Wilson’s disease, and bone marrow transplantation in mucopolysaccharidoses and immuno-osseous dysplasias.

### Research agenda
- Full genetic mapping of these disorders is required.
- Correction of the underlying molecular defect must be addressed.
- An analysis of the natural history of these illnesses in large study cohorts is necessary.
- Research is needed into prenatal diagnosis and genetic and occupational counselling.
- A study is required of the progression and outcome of premature OA in these diseases and the efficacy of corrective and joint replacement surgery.
- Controlled, multicentre trials need to address available and experimental treatments.
Acknowledgement

The authors gratefully acknowledge Mrs Katalin Dül-Szabó and Elizabeth Turra for their secretarial help, Mrs Mária Sándor, Mrs Mara Pollner and Mr László Szántó for their help in literature search, Professor György Fekete for providing the X-ray pictures of Fig. 1 and Mrs Mária Koltai for her technical assistance in photography.

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