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Spine in Patients with Diastrophic Dysplasia - a clinical and radiological study

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Academic dissertation

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To dreams of life and the endless fight for their fulfilment

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

The present thesis is based on the following original papers, which will be referred to in the text by their Roman numerals:

I Ville Remes, Eino Marttinen, Mikko Poussa, Ilkka Kaitila, Jari Peltonen. Cervical Kyphosis in Diastrophic Dysplasia. Spine 24:1990-5, 1999.

II Ville Remes, Pekka Tervahartiala, Mikko Poussa, Jari Peltonen. Cervical Spine in Diastrophic Dysplasia - An MRI analysis. J Pediatr Orthop 20:48-53, 2000

III Ville Remes, Mikko Poussa, Jari Peltonen. Scoliosis in Patients with Diastrophic Dysplasia - Natural History and a New Classification. Spine (submitted)

IV Ville Remes, Pekka Tervahartiala, Mikko Poussa, Jari Peltonen. Thoracic and Lumbar Spine in Diastrophic Dysplasia - A Clinical and MRI analysis. Spine (accepted for publication)

SUMMARY

Diastrophic dysplasia (DD) is an autosomally recessive type of skeletal dysplasia. Although rare worldwide, it constitutes the most common form of skeletal dysplasia in Finland. Typical clinical and radiological findings are short-limbed short stature, multiple joint contractures, early degeneration of the joints, spinal and foot deformities and dysmorphic ear lobes. Scoliosis, cervical kyphosis and exaggerated lumbar lordosis are often associated with DD.

The clinical and radiological severity of the spinal deformities varies greatly and information on the natural history is sparse. The pathogenic mechanism of these deformities is not fully known.

In the present study, 88 (55 female, 33 male) patients with DD underwent physical examination. Plain radiographs of the cervical spine were available for analysis for 120 (71 female, 49 male) patients and of the thoracic and the lumbar spine for 130 (77 female, 53 male) patients. Magnetic resonance (MR) images of the skull base and the cervical spine were available for 90 (57 female, 33 male) patients and of the thoracic and the lumbar spine for 88 (55 female, 33 male) patients. In age the patients ranged from new-borns to 78-year-olds at the time of the first radiograph or MR image. The average follow-up for all living patients with cervical kyphosis in the first radiograph (n=26) was 10.0 (range 3 – 32) years. Consecutive radiographs (two or more) of the whole spine were available for 105 patients (81%) with an average follow-up of 17.0 (range 2 – 41) years.

The degree of kyphosis, lordosis and/or scoliosis was measured from plain radiographs using Cobb's method. Magnetic resonance imaging (MRI) was used in analysis of the spinal cord, intervertebral discs, muscles and vertebrae. Transverse areas of the spinal cord were measured from C1 to Th2 and of the dural tube from C1 to Th2 and from L2 to S1.

Physical examination showed that the range of movement in the spine was reduced. The prevalence of cervical kyphosis was 24% (29/120). Among the patients whose first radiographs were taken before the age of 18 months, 96% (24/25) had kyphosis. It was first noted at an average age of 0.8 (range new-borns – 6.5) years in 29

patients. At that time the average curve of the deformity was 35 (range 6 – 130) degrees. Cervical vertebral body hypoplasia was associated with kyphosis. In 24 patients, the kyphosis resolved spontaneously at an average age of 7.1 years. Spontaneous resolution occurred if the kyphosis was less than 60 degrees (n = 24) in the first radiograph. Two patients had cervical kyphosis in the last follow-up (10 and 165 degrees). Three patients with severe kyphosis died: two of them before the age of 1 year and one at the age of 8 years.

The prevalence of scoliosis was 77% (100/130). The prevalence was even higher, 88% (84/96), in patients aged 16 or over. The frequency of scoliosis among females was 81% (62 /77) and among males 72% (38/53). There was no statistical difference in prevalence between genders. Scoliosis was 46 (range 11 – 188) degrees in the last radiograph. Scoliosis could be further divided into three subtypes: 1) early progressive (11 patients), 2) idiopathic (52 patients) and 3) mild, non-progressive (36 patients). One patient had a congenital scoliosis.

In MR images, the spinal canal was moderately narrowed, particularly in adults. The transverse areas of the medulla and of the dural tube were smaller than in the normal population ($p<0.0001$). One patient had severe thoracic and lumbar spinal stenosis. Five patients showed compression of neural structures in the lumbar spinal canal, but had no clinical symptoms. Compression of the medulla was associated with severe kyphosis (cervical or thoracolumbar) in three patients, but not with scoliosis in any of them (n=88). All patients exhibited narrowed disc heights and decreased signal intensity of the intervertebral discs. The prevalence of protrusions was low. Three patients had a prolapse in the lumbar spine. Two patients had vertebral anomalies (one wedge-shaped and one butterfly vertebra). All patients also manifested muscular atrophy and degenerative-like facet joint hypertrophy. The severity of these changes increased with age.

INTRODUCTION

Osteochondrodysplasias are rare, inherited disorders of the growing skeleton [64,81,113,121,158,159,179]. Over 150 different osteochondrodysplasias have been described [81,113]. Typical findings are dwarfism, often with disproportion between the lengths of the trunk and the limbs and skeletal deformities [81,179].

Diastrophic dysplasia (DD), previously often called diastrophic dwarfism, was first described as an entity by two French doctors, Lamy and Maroteaux, in 1960 [114]. Typical clinical and radiological findings include short-limbed short stature, multiple joint contractures and early degeneration of the joints, knee joint instability and spinal deformities such as scoliosis, cervical kyphosis and exaggerated lumbar lordosis [104,114,152,215]. Intelligence is normal [58,68,76,162]. Thus the main problems in everyday life are related to the orthopaedic complications of the disease.

DD is caused by mutations in a sulphate transporter gene (DTDST)[68]. The mutations are thought to result in impaired sulphate uptake of the cells and reduced proteoglycan sulphation, further causing abnormal growth of cartilaginous structures [82,172,175].

The present study focused on the spine. In physical examination the spine of DD patients is often rigid, and deformities such as scoliosis and cervical kyphosis are common. The most extensive studies have reported scoliosis in 37 – 88% of patients [152,205,215] and cervical kyphosis in one-third [152]. The clinical and radiological severity of these deformities varies greatly. Their pathogenic mechanism, however, is not known, and few data regarding the natural history of the deformities is available [104,152]. In addition, associated morphological changes in neural and soft tissue structures have not previously been studied in detail. Risk factors for progressive deformities are not known, nor have the timing and indications of treatment been established. The aim of this study, then, was to take a closer look at these issues.

REVIEW OF THE LITERATURE

Osteochondrodysplasias

Osteochondrodysplasias (skeletal dysplasias) are rare, inherited disorders of skeletal formation and linear growth. By definition, they involve disturbances of the cartilage components of the growing skeleton; however, other tissues may also be affected [64,81,113,121,158,159,179]. Over 150 different osteochondrodysplasias are currently recognised [81,113]. They are characterised clinically by skeletal deformities and varying degrees of dwarfism, typically with disproportion between trunk and limb lengths [81,113,121,158,159,179]. Some osteochondrodysplasias are apparent at or before birth (e.g. achondroplasia and diastrophic dysplasia) but others do not become evident for several years (e.g. pseudoachondroplasia) [81,121,158,159]. Their severity ranges from those incompatible with postnatal life (e.g. thanatophoric dysplasia) to those which are so mild that they are difficult to detect (e.g. spondyloepiphyseal dysplasia tarda) [81,121]. Thus, the osteochondrodysplasias are an extremely heterogeneous group of connective tissue disorders [81,158,159]. The prevalence of these dysplasias in the new-born infant is estimated to be between 3 and 4.5 per 10,000 births. Furthermore, the overall frequency of “lethal” skeletal dysplasias among perinatal deaths is about 9 per 1,000 [112].

In the majority of skeletal dysplasias, the inheritance is transferred in the autosomes by either dominant (e.g. achondroplasia and Kniest dysplasia) or recessive (e.g. diastrophic dysplasia and cartilage-hair hypoplasia) trait [81,159,179]. Some of the delineated conditions are sex-chromosome linked (for example X-linked spondyloepiphyseal tarda) [159]. This diversity points to a large number of genes essential to the proper development of cartilage and bone [68].

The skeletal dysplasias result form gene mutations that disrupt endochondral ossification, the process responsible for skeletal formation and linear growth [81,158]. Specifically, the target events include proliferation and terminal differentiation of growth plate chondrocytes and the coincidental genesis and modulation of the cartilage matrix that serves as a template for bone formation and gives rise to the articular surfaces of the joints [77,81].

Historical perspective

Short persons with abnormal body proportions can be identified in European and American art from ancient times [6]. However, it was not until 1878 that Parrot coined the term “achondroplasia” to distinguish these individuals from short persons with normal body proportions [143]. Fifty years later, Morquio in France and Brailsford in England separated them into two groups, those with predominantly short trunks and those with predominantly short limbs [6]. Until the 1960s, most disproportionate dwarfs were considered to have either achondroplasia (those with short limbs) or Morquio disease (those with a short trunk) [81,159]. During the 1950s, 1960s and 1970s many new osteochondrodysplasias were identified and described [103,114,117,124,125,129,183,188]. Delineating the diagnostic features (clinical manifestations, radiographic findings, inheritance patterns and morphology of the growth plate) received the greatest attention during this period. However, as this work continued, a gradual change of emphasis occurred, shifting the focus in the 1980s to defining the natural history and variability of the disorders [21,22,79,144,157,177,178,222] and in the 1990s to elucidating the mutations responsible for the disorders and characterising the pathogenic mechanism by which they disrupt bone growth [14,54,68,72,81,176,189,190,197].

Nomenclature and classification

The nomenclature traditionally used for skeletal dysplasias derives from a variety of sources and is based 1) on terms that attempt to describe the pathogenesis of the condition (e.g. achondroplasia and osteogenesis imperfecta), although they are sometimes inaccurate, 2) on a Greek term that describes the appearance of the bone or the course of the disease (e.g. thanatophoric (=death-seeking) dysplasia), 3) on recognition of the physician credited with the first description of the disorder (Larsen syndrome, Kniest dysplasia) or 4) on the part of the skeleton that is affected radiologically (e.g. spondyloepiphyseal dysplasia). [81,158,159,179] However, none of these radiographic distinctions necessarily reflect the extent of histological involvement.

Dwarfing conditions are frequently referred to as short-limb or short-trunk type, depending on whether trunk or limbs are more heavily involved [81,159,179]. Additional terms such as rhizomelic (proximal), mesomelic (middle) and acromelic (distal) are used to describe the segment of the limb with the greatest involvement in patients with

short-limbed dwarfism. These terms refer to the arm, forearm, and hand or thigh, leg, and foot regions, respectively [9,81,121,159,179].

A common tendency has been to split what was originally considered one condition into two or more. Modifiers such as congenita, tarda, dominant, recessive, X-linked and pseudo have been employed to distinguish such disorders and also to connote particular features [81].

The diversity of the skeletal dysplasias and the heterogeneity that may exist within a specific disorder have made classification difficult. In an attempt to develop a uniform nomenclature for these syndromes the International Nomenclature of Constitutional Diseases of Bone was proposed in 1970, and updated in 1977, 1983 and 1991 [81,158,159,179,182]. Five major groups were distinguished: 1) osteochondrodysplasias, 2) dystostoses, 3) idiopathic osteolyses, 4) chromosomal aberrations or primary metabolic abnormalities and 5) miscellaneous disorders with osseous involvement. In the last updating of the nomenclature newly described syndromes were added, and the disorders were organised into a clinically and a pathogenically based classification [182]. Thus disorders that share clinical, radiological and morphological features suggesting that they may be members of a family of disorders with a common pathogenic mechanism were grouped together. This classification will certainly be revised as the basic defect in each of these disorders is discovered [80,158,159].

Diastrophic dysplasia

Definition and classification criteria

Diastrophic dysplasia (DD) was first recognised as a separate entity in 1960 by Lamy and Maroteaux [114]. They borrowed the term ‘diastrophic’ from geology, diastrophism (*Greek* tortuous, twisted) being the process by which mountains, continents, ocean basins, etc., are formed through bending of the earth’s crust [2,76,214,215]. Even earlier descriptions of the disorder do exist, but in these the condition was misclassified as atypical achondroplasia [173,215] or achondroplasia with clubfoot. Cases were described under many different designations in the past, many of them misdiagnoses such as “atypical achondroplasia” and placed in the wastebasket of arthrogryposis multiplex congenita or chondrodystrophia in hospital diagnostic files [105,116,214]. Today,

DD can be reliably distinguished from other forms of skeletal dysplasias [76,187,214,219].

Typical clinical and radiological features of DD include short-limbed short stature, contractures and early degeneration in joints, unstable knee joints, spinal deformities such as scoliosis and cervical kyphosis, symphalangism and so-called “hitch-hikers” thumb, cleft palate, tracheo- and bronchomalasia, and deformed ear pinnae [76,79,104,215]. Intelligence is normal [68,105,162,187,219].

Prenatal diagnosis

The birth of an affected child into a family has usually awaked the parents‘ interest in prenatal diagnosis during the next pregnancy. DNA analysis provides a reliable means of prenatal diagnosis in the first trimester of pregnancy markers [70]. DNA can be obtained in parents from blood leukocytes and in children from cultured amnion cells or from chorion villus samples [70]. DNA markers have been used to predict the status of foetuses in families with a previous history of DD. The results predicted were concordant with those obtained by ultrasonography, and the phenotype of the foetus was correctly predicted in all cases [70].

Ultrasonography permits prenatal detection in the second trimester [91,94,95,123,137,153]. Skeletal defects occur at an early stage and are clinically diagnosable early in foetal development [94]. Due to the shortened long bone of the extremities, DD is an ideal form of skeletal dysplasia for prenatal diagnosis by ultrasonography [110], and has been used in women with or without known increased risk of the disorder [91,94,95,123,137,153]. The cornerstones of diagnosis have been abnormally short limbs and lateral projection of the thumbs on ultrasound examination.

Prenatal diagnosis of DD has also been performed by fetoscopy [94,137]. It is recommended, however, that this procedure should be reserved for problems that cannot be resolved by a non-invasive technique due to increased risk of procedure-related abortions and premature delivery [94].

Prevalence and incidence

The first observation of DD in the Finnish population was made by Perheentupa in

1972 [150]. The diagnosis has been confirmed in some 180 patients [128], making it the most common skeletal dysplasia in this country [93]. The incidence of DD in Finland is reported to be 1:33,000 [96], with one to three cases in new-borns yearly.

Genetic background

DD is caused by mutations in a sulphate transporter gene (DTDST, ***D***ias***t***rophic ***D***ysplasia ***S***ulphate ***T***ransporter)[68], which encodes for a sulphate transporter membrane protein. It is located in the distal long arm of chromosome 5 [69,71]. Over 25 different mutations in the DTDST gene have been identified [191]. The mutations are thought to result in impaired sulphate uptake of the cells and reduced proteoglycan sulphation, further causing structural and functional defects in the cartilage [68,82,172,175]. Reduced incorporation of inorganic sulphate has been found in cartilage and fibroblast samples [68,165,192]. However, the pathogenic mechanism of DD is not yet known.

In addition to DD, mutations in the DTDST gene are responsible for two other skeletal dysplasias: lethal achondrogenesis type IB and atelosteogenesis type II [72,190,192]. All these skeletal dysplasias arising at mutations in the DTDST gene have recessive inheritance and are currently classified as a DTDST-related family [192].

Cartilage morphology

Cartilage is abnormal in patients with DD. Histological, histochemical and ultrastructural studies have shown alterations in the growth plate and in articular, laryngeal, tracheal and ear cartilage [82,172,185]. In the resting cartilage, chondrocytes are reduced in number, enlarged and variable in shape and usually ovoid [82,154,172,175]. They show premature nuclear and cytoplasmic degeneration [82,172,175,185], and are surrounded by a halo of dense appearing, concentric cartilage matrix [82,154,175,185]. In the cartilage matrix, collagen is irregularly organised and distributed and there are abnormal fibrous areas where collagen fibrils are thickened, short and irregularly aggregated [82,172,175]. In addition, large cystic lesions are found in the matrix [82,154,172,175]. Staining with methods specific for sulphated proteoglycans indicates a deficiency of proteoglycans of the matrix [172]. In the growth zone, column formation appears regular [154,185], albeit short [82,185].

Short stature and growth

Severe short-limb dwarfism, already identifiable at birth, is a persistent feature of this disorder [2,64,73,76,79,111,116,128,214,215]. Scoliosis and hip and knee contractures further accentuate the apparent short stature [2,76,128,187]. Moreover, in relationship to trunk length the limbs are relatively short. Although all portions of the limbs are shortened, the proximal bones (humerus and femur) are relatively the shortest [187,215,219].

At birth, the median relative length is -3.0 SD or more below in both genders, indicating prenatal onset of the growth failure [128]. The usual pubertal growth spurt does not occur [76,128] although the other signs of puberty are normal [76]. The average adult height in skeletally mature patients with DD has been reported to be 135.7 (range 114.0 – 158.3) cm for males and 129.0 (range 98.0 – 143.0) cm for females. The averages are -7.2 and -6.7 SD below norms [128]. Growth failure has been reported to be even more severe [78,215]. The patients of these studies may present a more selected population, i.e. the severely affected or “Finnish” phenotype may be milder [128].

Spine

Typical deformities of the spine in patients with DD are scoliosis, cervical kyphosis and exaggerated lumbar lordosis [152,204,206,215]. In physical examination, mobility of the spine is often abnormally diminished [204]. Our knowledge of spinal abnormalities in DD is based largely on information obtained from plain radiographs [16,17,73,76,104,152,205,215].

Scoliosis

Scoliosis is more common in patients with DD than in the normal population with DD [152]. In the literature, the prevalence of the scoliosis has varied from 37 to 88% [152,205,215]. Scoliosis usually appears before the age of 5 to 6 years [2,17,76,104,105,127,206,219]. Accentuated kyphosis in the thoracic spine may or may not be associated with scoliosis [2,17,116,127,152,204,206]. The clinical and radiological severity of scoliosis varies [17,127,152,206,207,219].

In radiographs, the most common curve type has been lumbar [152]. Tolo et al. [205] found that 40% of patients with DD had deformities due to segmental defect in the thoracic spine. In other studies, this phenomenon has not been confirmed [73,152]. The curves can exceed 90 degrees in the early teens [104,152].

The outcome of treating scoliosis with braces have been poor [16,73,104,152], and early surgical intervention has been proposed by several authors [17,73,76,104,127,204,206,207]. In a study of 21 patients with DD, combined anterior and posterior fusion gave the best results in severe scoliosis [127].

Cervical kyphosis

Stover and al. [187] first described “a peculiar kyphosis of the cervical spine” shown in one patient in their series. Since then, several reports, usually with one to four patients with kyphosis, have been published [2,17,28,73,100,105,106,116,156,214]. In the largest series, cervical kyphosis was noted in one-third of patients with DD [152]. A study of the literature, shows that the natural history of cervical kyphosis is obscure. Both spontaneous resolution and severe progression of this deformity, causing even quadriplegia and death, have been reported in DD [17,53,73,76,100,104,106,116,152,204,207,215]. The pathogenic mechanism of the kyphosis is not known.

Cervical spine has been associated with hypoplasia of the mid-cervical vertebrae [17,73,100,116,152]. Two reports of MRI findings for two young patients with DD and severe cervical kyphosis causing cord compression [53,106] have been published.

Indications for the treatment of the kyphosis have not been established. In the literature, combined anterior and posterior fusion has been recommended [17,53,73,106,204,206].

Lumbar lordosis

Exaggerated lumbar lordosis is often noted [17,73,76,79,105,127,152,204,205,207,219] and has been suggested to be secondary to flexion contractures of the hips [17,127,152,205]. In radiographs, the lumbosacral angle is decreased, the average being 120 degrees [152].

Spinal stenosis

In some patients, the interpedicular distance in the lumbar spine is decreased [17,104,152,198,204,214]. Occasionally patients with thoracic and lumbar spinal stenosis, confirmed by positive myelography, have been reported [152]. However, no studies have been conducted on the prevalence or severity of spinal stenosis.

Lower extremities

Hips

At birth, the hips are congruent and MR images of new-born infants have shown no significant joint deformity [212]. Flexion contracture of the joint is usual and becomes evident as the child starts walking [2,104,149,198,212,219]. Flexion deformity of the hip is partly due to the abnormal shape of the femoral head and partly due to shortening of the flexors [104]. The range of rotational movements diminishes with age [212].

In radiographs, the appearance of the ossific nuclei of the proximal femoral epiphyses is clearly delayed [2,76,104,111,187,214,219]. In most patients the shape of the hip joint remains nearly spherical although there is clear overgrowth of the greater trochanter beyond the femoral head [104]. However, the femoral neck is short and broad and the femoral head is flattened in one-quarter of patients [76,104,111,198] appearing as the "double-hump" deformity [212]. Coxa vara has commonly been presented [2,7,76,104,187,198,215,219]. Signs of progressively severe degeneration may develop even before the capital femoral epiphysis ossifies [104]. Degenerative changes are progressive and thus hip deformity and premature osteoarthritis are the rule in patients with DD [7,104,149,166].

Intertrochanteric valgus-extension osteotomies have been performed in an effort to prevent progression of the osteoarthritis [7,104], but rarely can the natural history be altered by early surgical intervention [7]. Total hip replacement is the only solution in adulthood [104,149].

Knees

In contrast to other joints with contractures, knee joint instability is usually present [2,148,166,187,219] probably due to congenital defect of the ligaments [148]. The range of movement of the knee starts to diminish before the age of 5 years. Some patients have flexion contractures [148,187] and others hyperextension of knee [187].

Degenerative changes such as joint incongruity, unevenness of the subchondral bone and flattening of the bony epiphysis have been noted in radiographs of patients as young as 3 years, and the changes are accentuated with age [148]. The shape of the proximal tibia is better preserved than that of the distal femur, although anterior sloping of the tibial plateau has been noted in many cases [148]. The proximal

fibula is hypoplastic and short in relation to the proximal tibia in almost all patients [8,79,148,187,214,215]. The time of radiological appearance of the bony epiphysis of the patella is delayed. The patella is often inferiorly located and fragmented [148].

Patients with DD commonly need orthopaedic knee surgery, mainly due to severe osteoarthritis. Total knee replacement is the treatment of choice after growth. Some patients need surgery due to a congenitally dislocated patella to regain extension force in the knee [115]. However, according to Vaara et al., the whole anatomic complex of the femoral condyles and patella may rotate laterally [211]. Bilateral supracondylar osteotomies of the femur have been performed for the knee contractures but these frequently recur [215,219].

Foot

Foot deformities are common in patients with DD and can be seen in 93% of the patients [167]. Previously, the term “club foot” was often associated with DD [2,17,58,64,76,79,104,111,116,187,198,214]. However, there is great variation among the different types of foot deformity, which have been classified by Ryöppy et al. as follows: metatarsus adductus with (43%) or without (13%) tarsal valgus, equinus (8%) and equinovarus adductus (29%) [167].

The foot deformity is relatively refractory to surgical treatment [2,17,104,116,167,187,214,219]. Although use of the Ilizarov external fixation method to correct rigid deformities has given hope of better results [147]. Patients have great difficulty in finding shoes that fit [104,219].

Upper extremities

Shoulders and elbows

The main problem in the shoulder joint is limitation of movement [105,116,187,215,219]. The elbows frequently show contractures [2,8,17,76,104,105,116,187,198,214,215,219] and subluxation of the elbow joints has also been reported [76,111,116,215].

Hand

The hand deformity is one of the most characteristic features of this disorder [2,17,27,58,60,76,104,116,184,187,214,215]. The hands are short and broad and may present ulnar deviation due to shortening of the ulna [2,58,64,76,79,111,116,187,214,215]. The fingers are short and appear widely spaced with symphalangism, particularly of the proximal interphalangeal joints [2,76,79,104,105,111,187,198,214,215,219].

Characteristic is the 'hitchhiker' thumb [2,17,58,60,64,73,79,104,105,111,116,123,214,215]. Due to deformity of the first metacarpal, this feature leads to the clinical appearance of proximal insertion [58,76,104,111,123,198,214,215,219]. Thumbs are, in contrast to the fingers, hypermobile and usually broad [2,58,105,116,160,187,214,215,219]. The location of the thumb makes pinching difficult, for which the patient compensates by using the ulnar aspect of the proximal interphalangeal joint rather than the tip of the thumb [104] or by holding objects between the third and fourth fingers [187].

Craniofacial features

Facial appearance is often typical. The nasal bridge is narrow, with broad, flared nostrils and there is a characteristic circumoral fullness to the mouth [8,64]. A peculiar ear deformity is often noted [2,8,17,27,58,76,79,105,111,116,123,198,214,215,219] and can be seen in 84% of patients [215]. Swelling of the ears usually occurs within the first few days or weeks of life [8,76,116]. The pinnae swell and give an appearance of acute inflammation, often with cystic swelling and fluctuation [58,76,116,214,215]. After a period of three to four weeks, the swelling diminishes and the ear becomes hard, with thickening and deformity of the cartilage, which may later calcify and even ossify [2,17,58,73,76,116,187,214,215].

Cleft palate is a common finding [2,17,27,58,64,73,76,79,111,116,123,153,160,187,198,214,219]. Cleft palate has been recorded in 30 – 40% and submucous cleft palate in 12 – 26% of patients [160]. An open cleft palate is usually reconstructed in early childhood [160]. Most patients also have some degree of micrognathia [123,153,160,198,214].

Patients with laryngo-tracheal stenosis, or even extreme narrowing of the trachea, have been reported [215]. High pitched voice and misarticulation of the R, S or L sound are typical changes in speech [98,160]. A correlation between misarticulation and short maxilla has been reported [98].

Prognosis

Perinatal mortality is higher than normal population in patients with DD due to respiratory problems [28,55,60,64,68,70,76,105,150,160,215,219]. However, the life expectancy of individuals who survive early infancy appears to be good [105,150,187,215,219].

Except for the mildest cases, short stature, progressive, severe osteoarthritis, especially in the hip and knee joints, and spinal deformities result in a severe physical handicap [68,70,104,105,116,149,214,215,219]. Some patients are wheel-chair bound and, most have to undergo repeated orthopaedic surgery [68,104,167].

The health-related quality of life of patients is diminished [4,213]. Apart from the increased pain, this is mainly due to difficulties in moving and in managing the activities of independently, for example, reaching the buttons in a lift or the items on a shelf, or getting on a tram or a bus [213]. However, patients have great adaptability to deviations in health status [213].

Imaging of the spine

General aspects

The challenge in diagnostic imaging of the spine resides in the spine's complex osseous and soft tissue anatomy along with the myriad of disease processes that can affect it [74]. The spine can be evaluated by a number of different imaging modalities [11], for example, plain radiography, computed tomography (CT), scintigraphy and magnetic resonance imaging (MRI). Use of ultrasound in evaluation has been mainly limited to prenatal diagnosis [31,108,210]. Surface topographic imaging methods can be used to analyse the shape of the back surface [5,36,46,146,186,217,220].

Each of the modalities has specific advantages and disadvantages, and ultimately the individual clinical situation determines the procedure of choice. Common problems are numerous findings in different imaging studies of features seen also in asymptomatic people [19,37,56,61,88,92,142,221] and variable interobserver agreement about the interpretation of these findings [45,52].

In the evaluation of patients with spinal deformity, plain radiography is usually the primary method [121]. Evaluation sometimes requires assessment of the central spinal canal contents and the paraspinal soft tissue structures [63]. Owing to MRI's non-invasiveness and its superb soft-tissue contrast, it has largely replaced both myelography and CT myelography in evaluation of the spinal canal in patients with spinal deformity [62,63].

Plain radiography

Plain radiography is the basic diagnostic tool in the evaluation of the spine. The spinal radiograph still provides important information about problems with alignment, fractures and bony abnormalities and, by interference, it tells something about the disc [1,3,43,50,51,92,119]. The degree of scoliosis, lordosis and kyphosis can be measured from anteroposterior and lateral standing radiographs [38].

Advantages of plain radiographs are their low cost and ready availability. The biggest disadvantage of plain radiographs of the spine is radiation, especially to the gonads [101,119].

Computed tomography

Computed tomography (CT) is the preferred study in the evaluation of certain local bony abnormalities such as fractures and spondylolysis and -olisthesis [67,170,201]. In the cervical and the lumbar spine, it represents a cost-effective means of evaluating patients with radicular complaints in whom there is a suspicion of underlying disc herniation, bony foraminal or spinal stenosis [29,203].

Problems with claustrophobia and patient motion are fewer with CT than with MR imaging. Among the disadvantages of CT are its limitation to the axial plane. Three-dimensional images can be reconstructed, but the spatial resolution is not so good as with direct axial images. CT has relatively poor soft tissue contrast compared with MRI and is less sensitive and specific than MRI for numerous soft tissue abnormalities [62].

Scintigraphy

Scintigraphy can be used in screening evaluation. It is sensitive for stress fractures, metastasis and infection [40]. Disadvantages of the technique include its relatively poor spatial resolution and limited specificity.

Single-photon emission computed tomography (SPECT) has been shown to improve localisation and specificity, and is useful in detection of fresh pars defects [13,120]. There is also evidence that SPECT may aid in distinguishing between symptomatic and asymptomatic spondylolysis [39,57].

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has largely replaced CT and CT myelography in the routine evaluation of patients with spinal disorders [62], including those with degenerative disc disease [15,29,131-133,163,164,193], tumour [15,34,85,171,180,193,194], infection [48,151,180,193,200] and spinal deformities [47,118,135]. It can be used to evaluate post-traumatic patients to assess fracture and soft tissue complications [43,51,92,109,145,161,169,196,209].

MRI examinations of the spine usually include T1- and T2-weighted images [15]. Sur-

face coils can be used to achieve better resolution and paramagnetic contrast agents can be used to enhance soft tissues [15,24,41,89,122].

The major advantages of MRI are soft tissue contrast, direct multiplanar imaging and lack of ionising radiation [10,15,62,89]; the disadvantages are currently limited availability, and occasional difficulty in imaging large patients and patients with claustrophobia. Absolute contraindications to MR scanning include the presence of a pacemaker, a cochlear implant, older intracerebral aneurysm clips and metallic foreign bodies in the orbit [62]. Pregnancy, recent cardiac or vascular surgery and transcutaneous electrical nerve stimulators are relative contraindications [74]. The costs of MRI are currently about twice those of plain CT.

Surface topographic imaging

Surface topographic imaging methods register a three-dimensional description of the shape of the back [146,217]. It has been proposed that such methods could be used in the screening of scoliosis [5,46,217]. The presence, level and side of a scoliosis curvature can be demonstrated moderately well by back surface topography [186], but the correlation with the magnitude of scoliosis from topograms is not sufficient for most clinical purposes or decision-making [46,186].

AIMS OF THE PRESENT STUDY

The aims of the present study were:

1) to ascertain the prevalence and natural history of cervical kyphosis in patients with DD with a view to establishing whether there are prognostic factors which could help us to predict clinical outcome of the deformity;

2) to evaluate the prevalence and natural history of scoliosis and the distribution of different curve patterns in patients with DD;

3) to determine whether there is one group, or several groups, of patients with a similar curve pattern, rate of progression and age at onset of deformity;

4) to establish any aetiological factors for the high incidence of spinal deformities and diminished range of movements of the spine; and

5) to study changes in the spinal canal and medulla in this rare disease.

PATIENTS AND METHODS

Patients

The patients or their medical records accompanied by radiographs were referred to the Hospital for Children and Adolescents, Helsinki University Central Hospital, or to the Orton Orthopaedic Hospital of the Invalid Foundation, Helsinki, from all over Finland in 1961 – 1997 (Figure 1, Table 1). The diagnosis of diastrophic dysplasia (DD) was based on established clinical and radiological findings of DD [114,215]. The diagnosis was confirmed by the same clinical geneticist with experience in skeletal dysplasias.

Paper	I	II	III	IV
Study design	Partially prospective	Cross-sectional	Partially prospective	Cross-sectional
Type of data	Radiographical	MRI	Radiographical	Clinical and MRI
Patients	120	90	130[2]	88
Females	71	57	77	55
Males	49	33	53	33
Average age (years)	19	31	16[3]	31
Range (years)	0 – 63	0 – 56	0 – 78	3 – 56
Follow up, N	69[1] (58%)		105 (81%)	
Average (years)	10[1]		17	
Range	3 – 32		2 – 41	

TABLE 1. Summary of study design, type of data, patients and follow-up time. [1]All living patients with cervical kyphosis in the first radiograph (n=26) were followed for an average of 10 years. [2]Eight families had two affected adult siblings, and three families had three affected adult siblings. [3]Ninety-six (74%) of the patients were over 16 at the time of the last radiograph.

Of the 130 patients included in the paper III, eight had undergone surgical treatment of the thoracic and/or lumbar deformity. Only radiographs taken before operation were included. Three of these eight patients were also included in MRI study (IV). Of the 88 patients included in the study IV, two had undergone surgical treatment for the lumbar spinal stenosis.

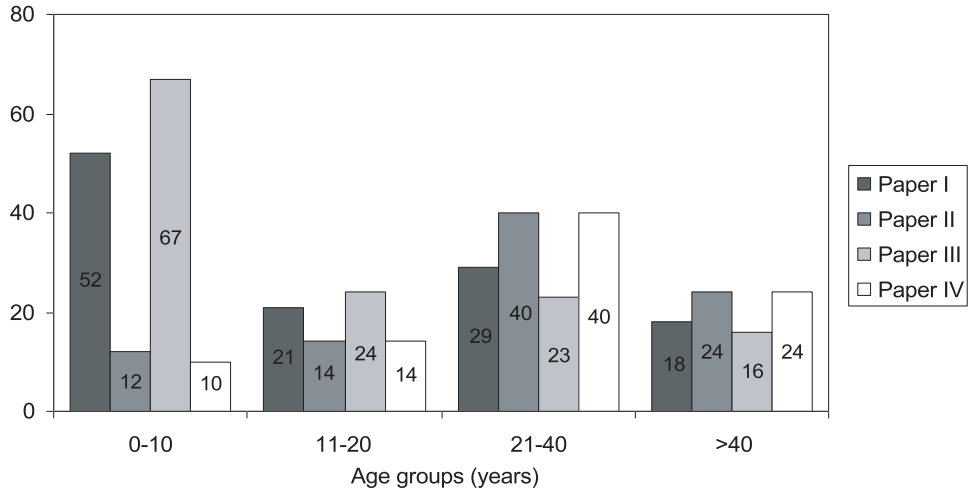

FIGURE 1. Number of patients in each study (papers I-IV) in different age groups at the time of the first radiographs or MR images.

Methods

Clinical data (study IV)

The patients underwent clinical examination between June 1996 and March 1998. In addition to questions soliciting demographic data, they were asked if they had had low back pain (LBP) during the last 3 months (yes/no). On physical examination, thoracic kyphosis and lumbar lordosis were evaluated on a subjective arbitrary scale with three grades: 1) exaggerated 2) normal and 3) straightened. Scoliosis, if present, was recorded. The degree of rib hump was measured with a scoliometer [32]. The distance from finger tips to floor in forward bending was measured and spinal mobility was visually evaluated. The degree of functional leg length discrepancy, if any, was measured with wooden blocks placed under the shorter leg.

Radiographic data (studies I and III)

Spinal deformities (cervical kyphosis and scoliosis)

Radiographs

Anteroposterior and lateral radiographs of the cervical and the whole spine were taken in an upright position. One hundred patients also had bending radiographs of

the cervical spine. The youngest patients were radiographed supine. The radiographs were obtained as part of a systematic radiological evaluation. All living patients who had cervical kyphosis in the first radiograph (n=26)were followed for an average of 10.0 (range 3 – 32) years. Consecutive radiographs (two or more) of the whole spine were available for 105 patients (81%) with an average follow-up of 17.0 (range 2 – 41) years.

Measurements

The degree of kyphosis or lordosis in the cervical spine or scoliosis, if any, in the thoracic and/or lumbar spine was measured by Cobb´s method [38] (Figure 2). Anterior or posterior displacement of cervical vertebrae was measured from the lower posterior corner of the upper vertebra to the upper posterior corner of the lower vertebra. Rotation of the thoracic and lumbar vertebrae (yes/no) in association with scoliosis was evaluated visually from the position of the spinous process.

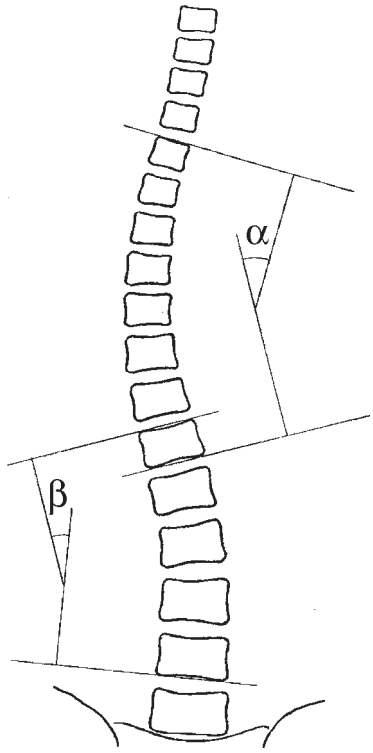

FIGURE 2. Schematic presentation of Cobb's method. Kyphosis and lordosis were measured in a similar way.

Definitions

Cervical kyphosis was defined as a local, posterior curve exceeding five degrees. It was regarded as severe if it was more than 60 degrees. Kypholordosis was a mild local kyphosis in the upper cervical spine followed by a lordotic segment in the lower cervical spine with four-cornered vertebral bodies. A lateral curve of more than 10 degrees was regarded as scoliosis.

The criteria of vertebral hypoplasia was triangular or round form of the vertebral body with decreased sagittal diameter. The limit of posterior displacement was a step-off exceeding 3 mm between the lower posterior corner of the upper vertebra and the upper posterior corner of the lower vertebra.

Criteria for classification of scoliosis

Curves were primarily classified according to King [102]. However, not all curves fit this classification, and thus curves were also classified according to the system introduced by Coonrad et al. [42]. Intrafamilial variation in the degree and curve pattern of the scoliosis was also investigated.

King's classification [102]

Type I

S-shaped curve in which both thoracic and lumbar curve cross midline. Lumbar curve larger than thoracic curve on standing radiograph. Flexibility index a negative value (thoracic curve ^{3} lumbar curve on standing radiograph, but more flexible on side-bending).

Type II

S-shaped curve in which thoracic and lumbar curve cross midline. Thoracic curve larger than lumbar curve on standing radiograph. Flexibility index a positive value.

Type III

Thoracic curve in which lumbar curve does not cross midline (so-called overhanging).

Type IV

Long thoracic curve in which L5 is centred over sacrum but L4 tilts into long thoracic curve.

Type V

Double throracic curve with T1 tilted into convexity of upper curve. Upper curve structural on side-bending.

Coonrad's classification [42]

Type 1A

Double structural thoracic and lumbar curve pattern, with a larger and less flexible lower curve that has an apex at or below the L1-L2 disc space.

Type 1B

Double structural thoracic and thoracolumbar curve pattern, with a larger and/or less flexible lower curve that has an apex at T12, L1 or the interspace between.

Type 2A

A double structural thoracic and lumbar curve pattern, with a larger and/or less flexible upper curve, and with the apex of the lower curve at or below the L1-L2 disc space.

Type 2B

Double structural thoracic and thoracolumbar curve pattern, with a larger and/or less flexible upper curve, and with the apex of the lower curve at T12, L1 or the interspace between.

Type 3

Single structural thoracic curve with the apex usually at T7, T8 or T9.

Type 4

Single structural thoracic curve, usually with a lower apex than type 3, commonly at either T10 or T11, the lower end vertebra usually at L2 or L3, and with L4 always tilted into the curve.

Type 5
Double structural thoracic curve pattern with T1 or T2 usually tilted into the upper curve, with the apices of both curves at the thoracic level.

Type 6
Single thoracolumbar curve pattern with the apex always at T12, L1, or the inter-space between.

Type 7
Single lumbar curve pattern with the apex at or below the L1-L2 disc space, to the level of the L4-L5 disc space.

Type 8
Triple curve pattern, with laterality determined by the size of the largest of the three curves.

Type 9
Quadruple or multicurve pattern.

In a trial to classify patients with similar curve patterns, age at the onset of scoliosis, the rate of progression and the magnitude of the scoliosis at the end of growth were noted.

MRI data (studies II and IV)

MR images of the skull base, and of the cervical, the thoracic and the lumbar spine were systematically taken between June 1996 and March 1998. Patients with MR images of the cervical spine were divided into four age groups: 0 – 10, 11 – 20, 21 – 40 and 41 – 60 years, with 12, 14, 40 and 24 patients, respectively. The patients with MR images of the thoracic and the lumbar spine were grouped in the same way, except that there were 10 patients in the age group 0 – 10 years.

The MR images of the cervical spine were taken in 32 patients with a 1.0 T and in 58 patients with a 1.5 T superconducting imager (Siemens Magnetom Expert 1T and Siemens Magnetom Vision 1.5 T, Siemens AG, Erlangen, Germany). The corre-

sponding numbers for the thoracic and the lumbar spine were 31 (1.0 T) and 57 (1.5 T). A local coil was used in all studies. T1-weighted spin echo and T2-weighted fast spin echo sequences were used in the sagittal direction with a slice thickness of 3 or 4 mm. T1-weighted images were acquired at the coronal plane. In addition, T1-weighted axial images were obtained at the level of the skull base and from each intervertebral disc. The slices were angled perpendicular to the long axis of the canal.

A pilot study with five patients was carried out in June 1996. Defined on the basis of these results, the final parameters to be measured were the following.

Skull base

The relative size of the foramen magnum was estimated and stenosis was defined as a medullar compression at the level of the skull base. The distance from tip of dens to Chamberlain's line was measured. Chamberlain's line was drawn between the posterior pole of the hard palate and the posterior margin of the foramen magnum [181]. The structure and signal intensity of the medulla oblongata and cerebellar tonsils were evaluated.

Spinal cord and canal

The course, shape and signal intensity of the spinal cord were assessed. The transverse areas of the spinal cord from C2 to C7 [139] and of the dural tube from C2 to C7 [139] and from L2 to S1 [65] were measured (Figure 3) from T1-weighted axial MR images at the level of the intervertebral disc using a GE Advanced Windows workstation (GE Medical Systems, Milwaukee, Wisconsin, USA). The areas were measured three times and the average was then calculated. The measurements were made on the cervical spine of patients aged 20 years or over and on the lumbar spine of patients aged 15 years or over. Measurements from decompressed levels in two patients were not included in the analysis. These data were compared with the reference values reported in the literature [65,139]. The size of the spinal canal from C2 to S1 was evaluated on an arbitrary scale with four grades: 1) normal amount of cerebrospinal fluid (CSF) around the medulla, 2) decrease in CSF around the medulla, 3) no CSF around the medulla and 4) medullar compression.

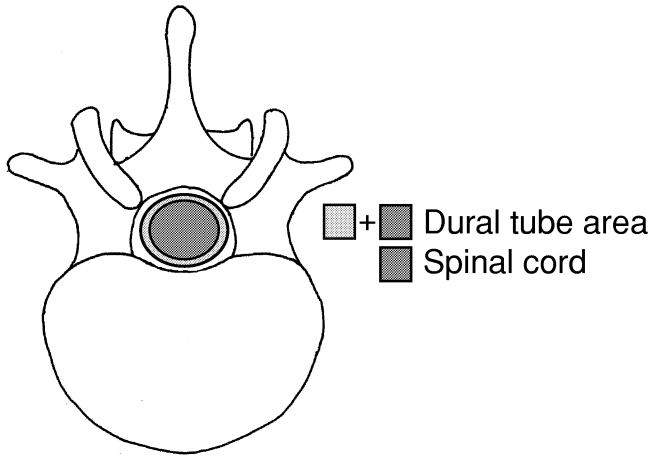

FIGURE 3. Schematic presentation of measurement of the spinal cord and the dural tube areas.

Intervertebral discs

Disc height was assessed visually (normal / decreased). Disc protrusion was recorded if the disc extended beyond the confines of the vertebral bodies including bony spurs. Disc protrusions were classified as 1) a bulge, a small, diffuse, circumferential symmetric extension of the disc or 2) a prolapse, a focal or asymmetric extrusion [19,88]. A decrease, if any, in signal intensity of intervertebral discs on T2-weighted images was noted. Discs were classified as normal (bright), speckled or black [20,126].

Vertebrae and spinal alignment

Sagittal alignment of the cervical spine and coronal alignment of the thoracolumbar spine were recorded from radiographs taken on the same day. The shape of the vertebrae and facet joints was assessed for any anomalies and degenerative changes such as bony spurs and facet joint hypertrophy. Schmorl's nodes, defined as herniation of the disc into the vertebral body end-plate, and bone marrow changes were noted. Bone marrow changes were classified according to Modic et al. [133] as type I, defined as decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images, or type II, defined as increased signal intensity on T1-weighted images and isointense or slightly increased signal intensity on T2-weighted images.

Muscles

The status of the psoas and back muscles in the lumbar spine was assessed from the T1-weighted axial images. The back muscles, that is, the erector spinae and multifidus, were assessed together. The evaluation took place in two ways: by visually comparing the cross-section of the muscles with the diameter of the nearby vertebral body and by assessing the amount of high signal intensity streaks, representing fat in the muscle mass [141,142]. An arbitrary scale with three grades was used: 1) normal (normal volume, no fat), 2) mild atrophy (psoas: slightly to moderately decreased volume, no fat; back muscles, slightly to moderately decreased volume, slight to moderate amount of fat), and 3) severe atrophy (psoas: severely decreased volume, no fat; back muscles, severely decreased volume, abundant amount of fat).

Intra- and interobserver error

To minimise the risk of intra- and interobserver error [155] all MR images were read together at least twice by two of the authors (VR and PT). The evaluation was based on a consensus decision and, in borderline cases, the milder option was chosen.

Statistical methods

The statistical analysis of the prevalence of the various abnormalities and the area measurements were performed by chi-square analysis and Student's t-test, respectively. Where the expected counts were low, less than five, Fisher's exact test replaced the chi-square analysis [35]. The statistically significant p-value was defined as $p<0.05$ and the highly significant value as $p<0.01$.

Ethical considerations

The informed written consent of all participants was obtained from the patients themselves or from their parents if patients were under 18. The present study was accepted by the ethical committees of Hospital for Children and Adolescents, Helsinki University Central Hospital, and Orton Orthopaedic Hospital.

RESULTS

Clinical data

Low back pain history

The low back pain (LBP) was mild and age-dependent. None of the young patients, under the age of 21 years (n=24), complained of LBP, but it was quite common in older age groups: nine (23%) of the patients aged 21 – 40 years and nine (42%) of those aged 41 – 60 had LBP. All, however, reported that the pain was mild.

Physical examination

Scoliosis was common and spine mobility was restricted, as indicated by physical examination. Scoliosis was clinically evident in the thoracic spine in 40 (45%) and in the lumbar spine in 35 (40%) of the 88 patients. The average rib hump was 12 (range 5 – 22) degrees in the thoracic and 9 (range 3 – 22) degrees in the lumbar spine. Thoracic kyphosis was straightened in 40 (45%) and exaggerated in 13 (15%) patients. Lumbar lordosis was straightened in 22 (25%) and exaggerated in 31 (35%) patients. Half of the patients (42/84) stood in a stooping position and four were not able to stand at all but needed a wheel-chair. Of the 88 patients, 72 (82%) were able to stand without support and to bend forward without losing their balance. In these patients, the mean distance from finger tips to floor was 13 (range 0 – 40) cm. Their spine was often rigid and movement in forward bending usually occurred in the hip joints. The remaining 16 (18%) patients were either wheel-chair bound (n=4) or had problems standing without support due to flexion contractures of the hips and knees and/or foot deformities. Functional leg length discrepancy, average 2.4 (range 1 – 5.5) cm, was noted clinically in 23 of 84 (27%) patients.

Radiographic data

Prevalence of cervical kyphosis

Cervical kyphosis was evident in 29 out of 120 (24%) patients (Figure 4). The first radiographs were taken of 25 patients before the age of 18 months; 24 (96%) of them had cervical kyphosis. The first radiographs had been taken of another 47 patients at the age of 20 years or later; none of them had cervical kyphosis, but two (4%) had cervical kypholordosis (“swan-neck”)

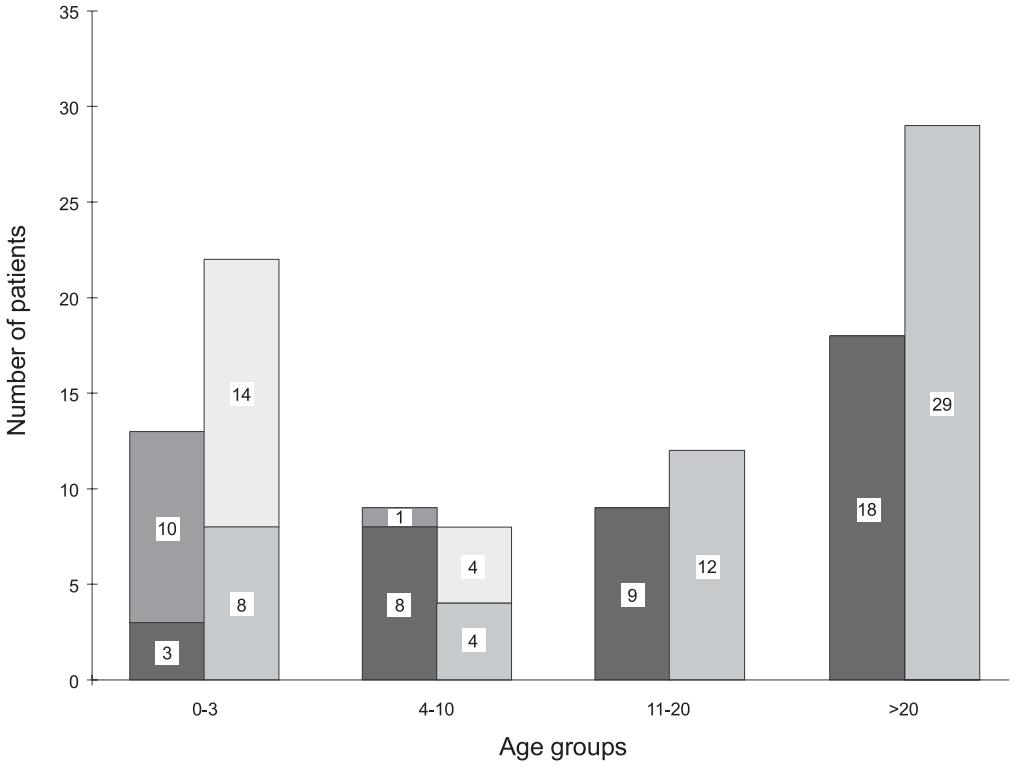

FIGURE 4. Number of patients in each age group. Dark columns indicate males. In the first two age groups the tops of columns indicate the number of patients with cervical kyphosis in their first radiograph.

Severity of kyphosis

In all cases cervical kyphosis was the primary deformity. It was first noted at an average age of 0.8 (range new-borns – 6.5) years in 29 patients. At that time the average curve was 35 (range 6 – 130) degrees. The development of the kyphosis during growth in 29 patients is shown in Figure 5. In the four most severe cases the kyphosis exceeded 60 degrees and the dens was parallel to the base of the occiput (Figure 6d). The kyphosis was also evident in bending radiographs suggesting, a structural deformity. Atlantoaxial instability was not noted in any bending radiographs.

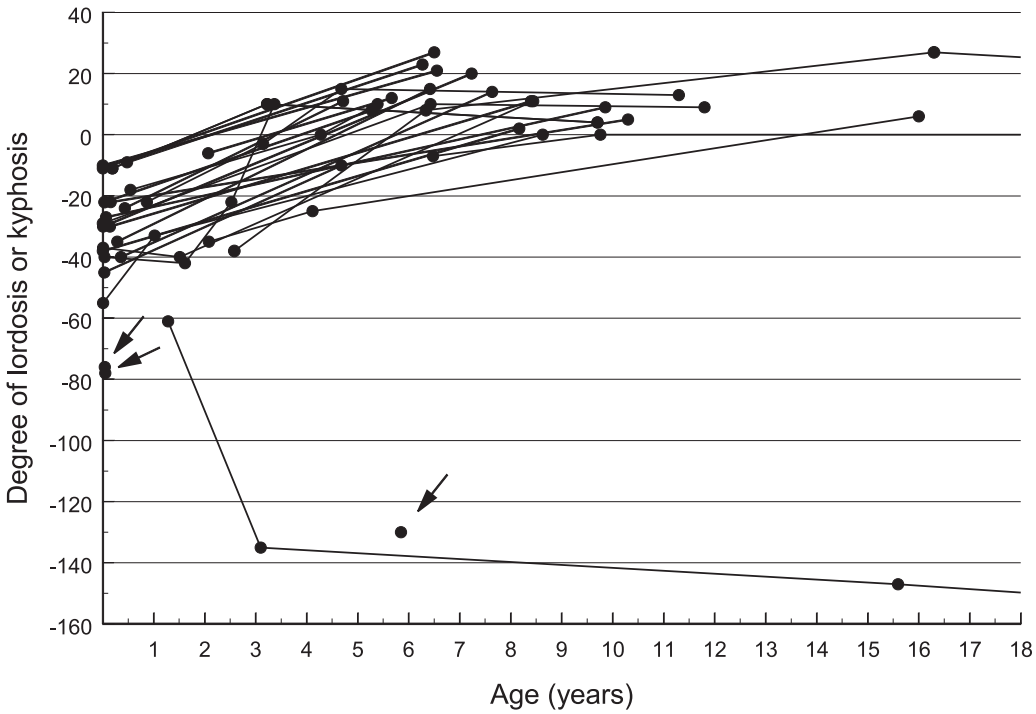

FIGURE 5. Development of kyphosis during growth in 29 patients with kyphosis in their first radiograph. Kyphosis is marked as a negative angle and lordosis as a positive angle. One circle indicates one radiograph. Arrows indicate deceased patients.

Location of kyphosis and vertebral hypoplasia

The location of the kyphosis was mid-cervical with the apex at C3 or C4 and occasionally at C5. Hypoplasia of the vertebral bodies, C3, C4 and/or C5, was always linked to kyphosis (Figures 6 and 7). The apex vertebra was triangular or round.

Displacement of the vertebrae

Posterior displacement is associated with the magnitude of the kyphosis. When spontaneous resolution occurred, posterior displacement disappeared. In radiographs taken of 25 patients at different times, posterior displacement of 4 – 5 mm of the apex vertebra was shown in 13 of 14 neutral radiographs showing kyphosis of 30 to 60 degrees, in 6 of 9 radiographs showing kyphosis of 15 to 29 degrees, and in 2 of 10 radiographs showing kyphosis of less than 15 degrees. In the most severe cases (kyphosis greater than 60 degrees) it was not possible to measure the posterior displacement due to the severely deformed structure of the cervical spine (Figure 6).

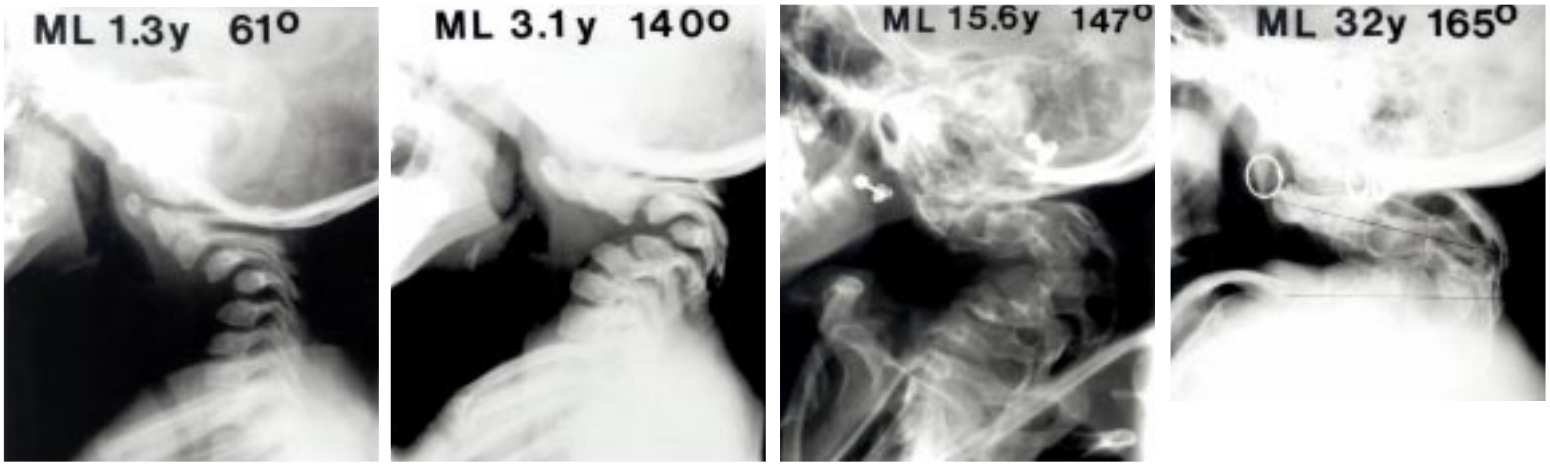

FIGURE 6.The most severe case of cervical kyphosis A) At the age of 1.3 years kyphosis was 61 degrees, B) at 3.1 years 140 degrees, C) at 15.6 years 147 degrees, and D) at 32 years 165 degrees. Note the rapid progression of kyphosis and the marked hypoplasia of the vertebral body of C3 to C5.

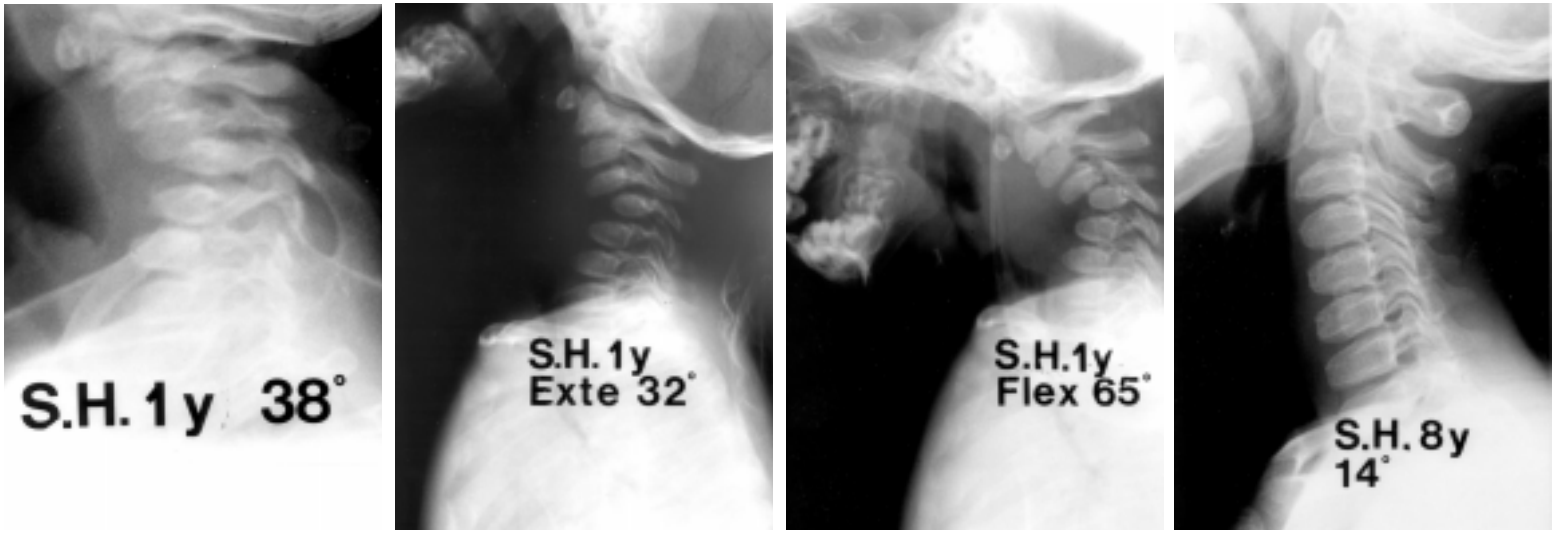

FIGURE 7. An example of spontaneous resolution of cervical kyphosis. A), B) and C) At the age of one year kyphosis was 38 degrees in neutral position, 32 degrees in extension and 65 degrees in flexion. There is no resolution in the bending radiographs suggesting a structural deformity. D) At the age of 8 years lordosis 14 degrees. Note the spontaneous resolution of vertebral body hypoplasia of C4.

Natural history of the cervical kyphosis

The kyphosis resolved spontaneously by the age of 7.1 years on average. In 11 patients, who underwent more systematic radiological follow-up during the first decade of life, the resolution occurred before the age of 5 to 6 years. Spontaneous resolution occurred if the kyphosis was less than 60 degrees (n = 24) in the first radiograph (Figure 5 and 7).

The kyphosis persisted in five patients. Two of these patients are alive: one patient had a severe 165-degree kyphosis at the age of 32 years (Figure 6). The other, a 4-year-old child with an initial curve of 55 degrees, had a 10-degree kyphosis at the last follow-up. Three patients with severe kyphosis died. Two of them, with a 65-degree and 76-degree kyphosis, died before the age of 1 year. They also had severe tracheo- and bronchomalasia. Decompression and an anterior and posterior fusion were performed on the patient with the 76-degree kyphosis without subsequent relief of her symptoms, muscle weakness or respiratory problems. The third patient, with a 130-degree kyphosis, had no neurological symptoms. He became quadriplegic during anaesthesia for a foot operation at the age of 8 years and died of cardiorespiratory failure 6 months later.

Prevalence of the scoliosis

Of the 130 patients, 100 (77%) had scoliosis. When compared with the normal population [216], the difference was highly significant ($p < 0.001$). The prevalence of scoliosis was even higher, 88% (84/96), in patients aged 16 years or over. The frequency of scoliosis among females was 81% (62 /77) and among males 72% (38/53). There was no statistical difference in prevalence between genders.

Curve patterns

Eleven (11%) patients had severe scoliosis. In the last radiograph (Figure 8d) the curves of these patients resembled each other. Scoliosis was evident at the age of 3 years or earlier in four patients with follow-up radiographs taken at that age. The deformity was initiated as a low thoracic (apex Th 10-11) or thoracolumbar (apex Th12-L1) curve, starting with a tilting of the L3 or L4 vertebra (Figure 8a-b). Rotation was marked. Six patients with radiographs from early childhood showed rapid deterioration of curves at follow-up. The curves averaged 134 (range 83 – 188) degrees in the last radiograph (Table 2). The convexity of the curves was to the right in four and in the left in seven patients. In the lateral view, severe kyphosis with an average

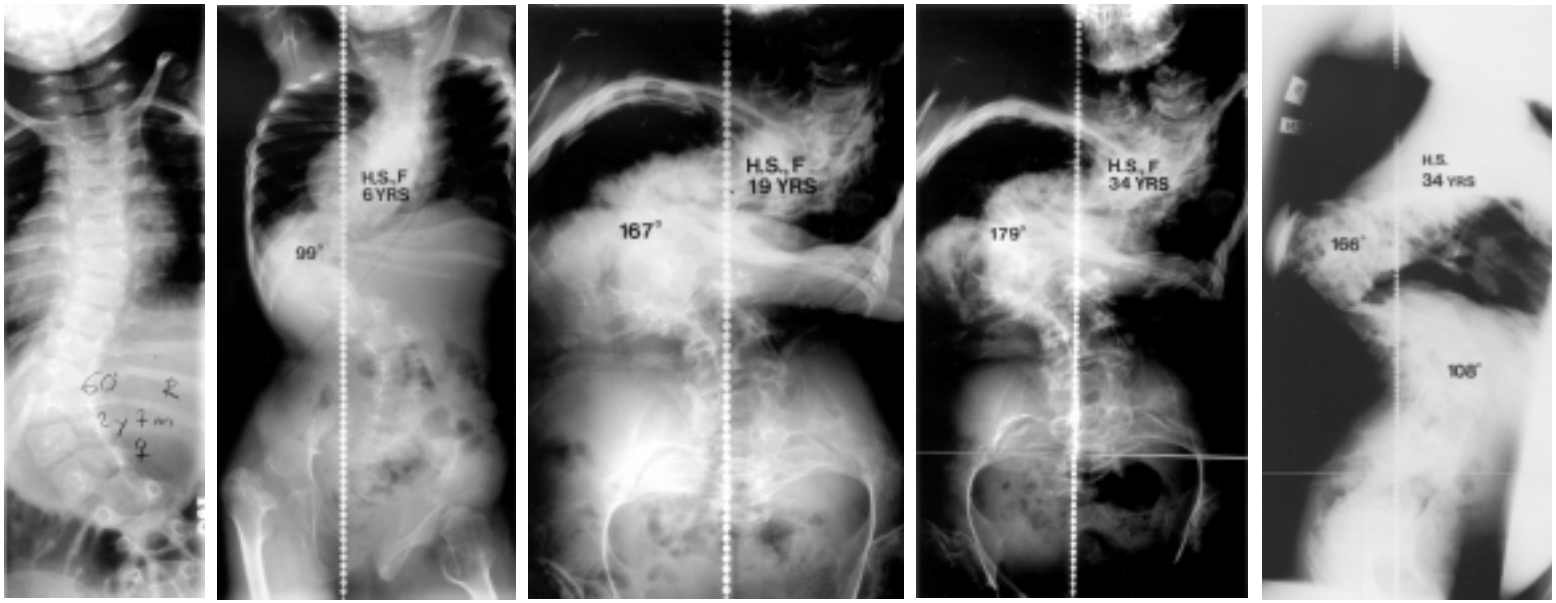

FIGURE 8a-e. An example of the early progressive type of scoliosis. a) At the age of 2 years and 7 months scoliosis was 60 degrees. Note the severe rotation in the lumbar spine. The apex of the scoliosis is T12. b) At 6 years scoliosis was 99 degrees; the apex is now T8. c) At 19 years scoliosis has progressed to 167 degrees. d-e) Subsequent progression was slight and at 34 years scoliosis was 179 degrees. In the lateral view, severe kyphosis of 166 degrees was noted.

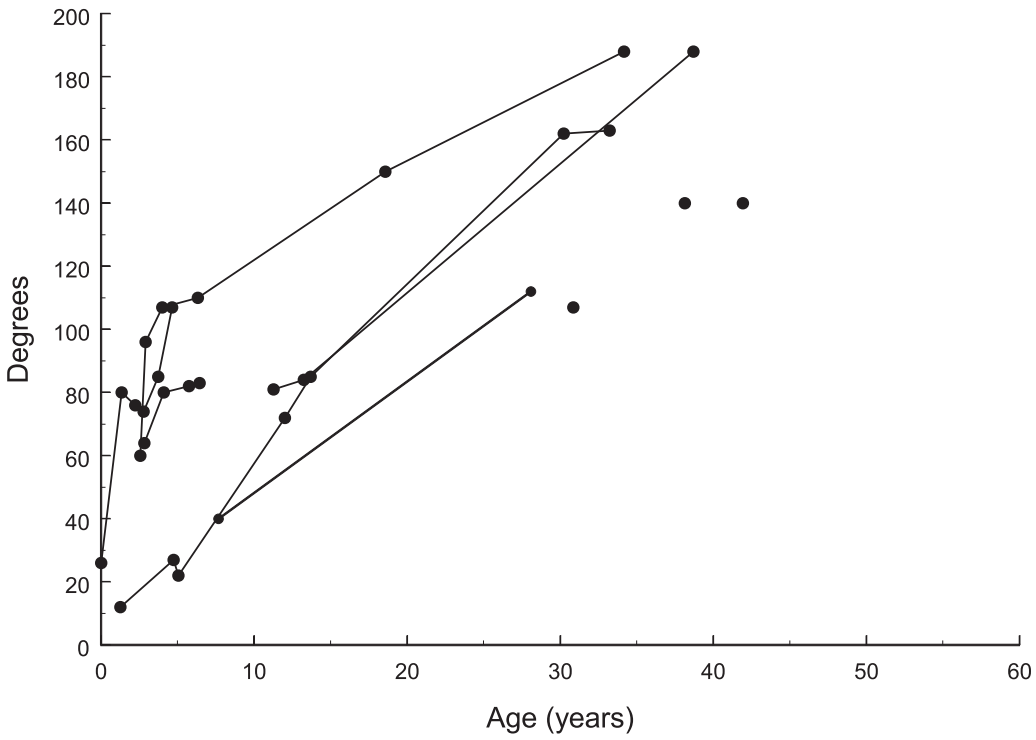

FIGURE 9. Natural history of early progressive type of scoliosis from birth to 60 years. One circle is one radiograph.

of 97 (range 40 – 166) degrees was seen. The apex was located at the lower thoracic spine or at the thoracolumbar junction. The development of these curves is shown in Figure 9.

Curve patterns similar to those in adolescent idiopathic scoliosis were seen in 52 (52%) patients (Figure 10). The curves were usually evident before the age of 10 (range 3 –16) years in 32 patients with follow-up radiographs from childhood. Progression of the curves was mild to moderate in these patients. The degree of rotation to convexity seemed to be related to the severity of the deformity. The curve magnitude was usually at least 20 degrees (n=50) at the last follow-up. Curves averaged 46 (range 16 – 104) degrees in the last radiograph (Table 2). Only two of 41 (5%) patients had a curve of more than 100 degrees in adulthood. In the lateral view, thoracic and lumbar alignment varied among patients. In the thoracic spine, the average kyphosis was 30 (range 2 – 100) degrees. In the lumbar spine, the average

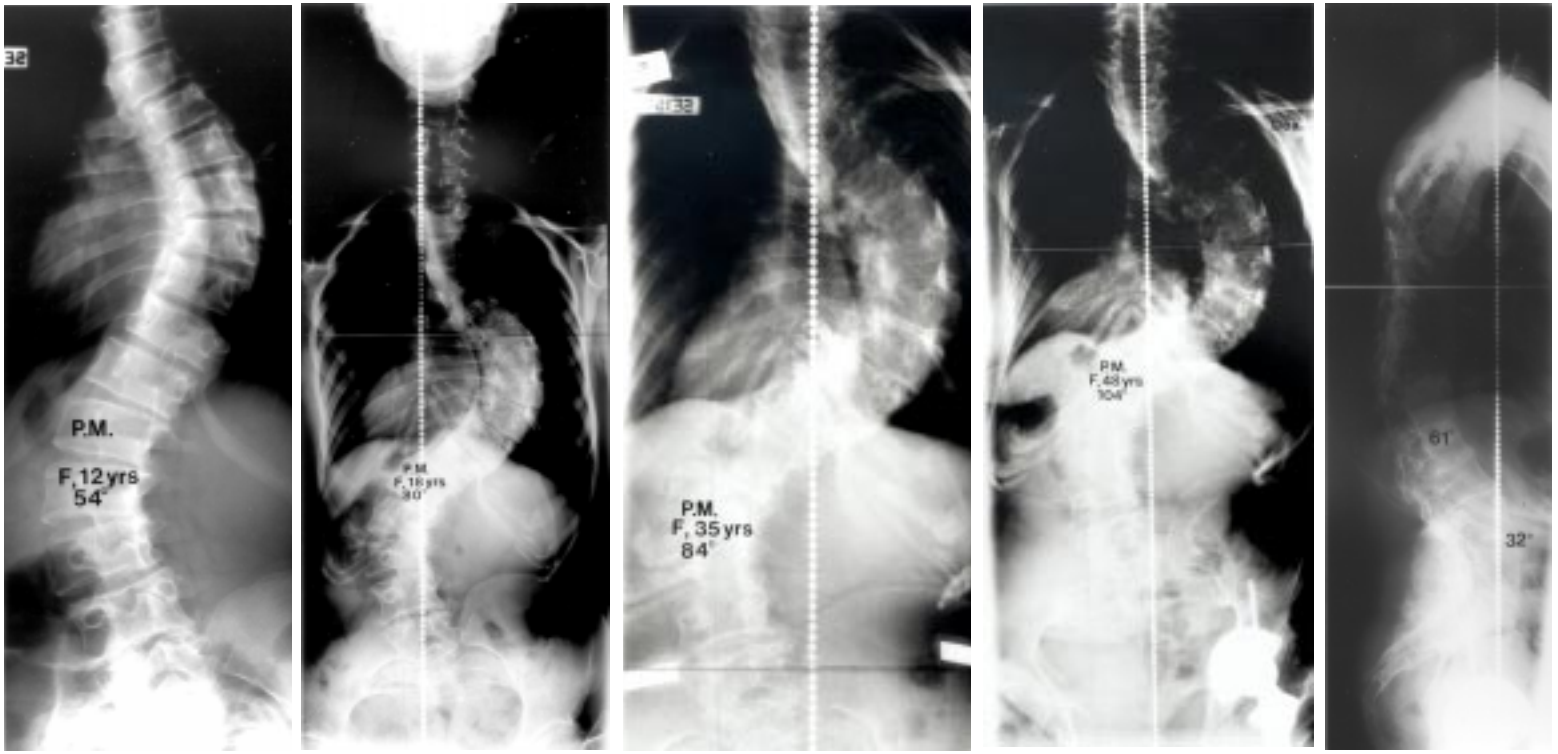

FIGURE 10a-e. An example of the idiopathic type of scoliosis. a) At the age of 12 years scoliosis was 54 degrees, b) at 18 years 80 degrees and c) at 35 years 84 degrees. d) In the last radiograph, at the age of 48 years, scoliosis was 104 degrees. e) At the same age in the lateral view, kyphosis was 61 degrees and lordosis 26 degrees.

			Last radiograph					
Type	n	n1	age (yr)	range (yr)	average	range	f-u	range
Early progressive	11	4	37	5 – 78	134º	83º – 188º	20	4 – 32
Idiopathic-like	52	3	30	4 – 63	46º	16º – 104º	18	2 – 37
Mild non-progressive	36	9	35	7 – 56	18º	11º – 40º	20	2 – 41

TABLE 2. Age of patients and degree of curve at the time of the last radiograph, and follow-up time in different subgroups. n = number of patients, n1 = number of patients with only one radiograph, range = range of age / curve / follow-up, average = average degree of curves, and f-u = follow-up time in different subgroups. For two patients with early progressive and four with idiopathic-like type of scoliosis, the last radiograph before surgery is given.

lordosis was 34 (range 2 – 112) degrees. In addition, 14 patients had a quadruple curve pattern in the thoracolumbar spine (kyphosis-lordosis-kyphosis-lordosis or lordosis-kyphosis-lordosis-kyphosis). The average lordosis in the upper (n=1) or the lower (n=13) thoracic spine was 13 (range 4 – 21) degrees and the average kyphosis in the upper (n=13) or the lower lumbar spine (n=1) was 19 (range 2 – 60) degrees. Curves of the Idiopathic-like type were further categorised according to King's and Coonrad's classifications (Table 3). The natural history of these curves is shown in Figure 11.

KING (type)	Coonrad (type)	Left / Right	Total (%)
I	1 A	8 / 1	9 (17%)
	1 B	1 / 0	1 (2%)
II	2 A	1 / 7	8 (15%)
	2 B	2 / 1	3 (6%)
III	3	2 / 7	9 (17%)
IV	4	4 / 3	7 (13%)
V	5	1 / 2	3 (6%)
	6	4 / 1	5 (10%)
	7	2 / 1	3 (6%)
	8	0 / 1	1 (2%)
	9	3 / 0	3 (6%)
Total		28 / 24	52 (100%)

TABLE 3. Categories of idiopathic-like type of scoliosis according to King's and Coonrad's classifications. L / R = number of patients with scoliosis convex to left and right, Total = total number and percentage of patients with scoliosis in each type.

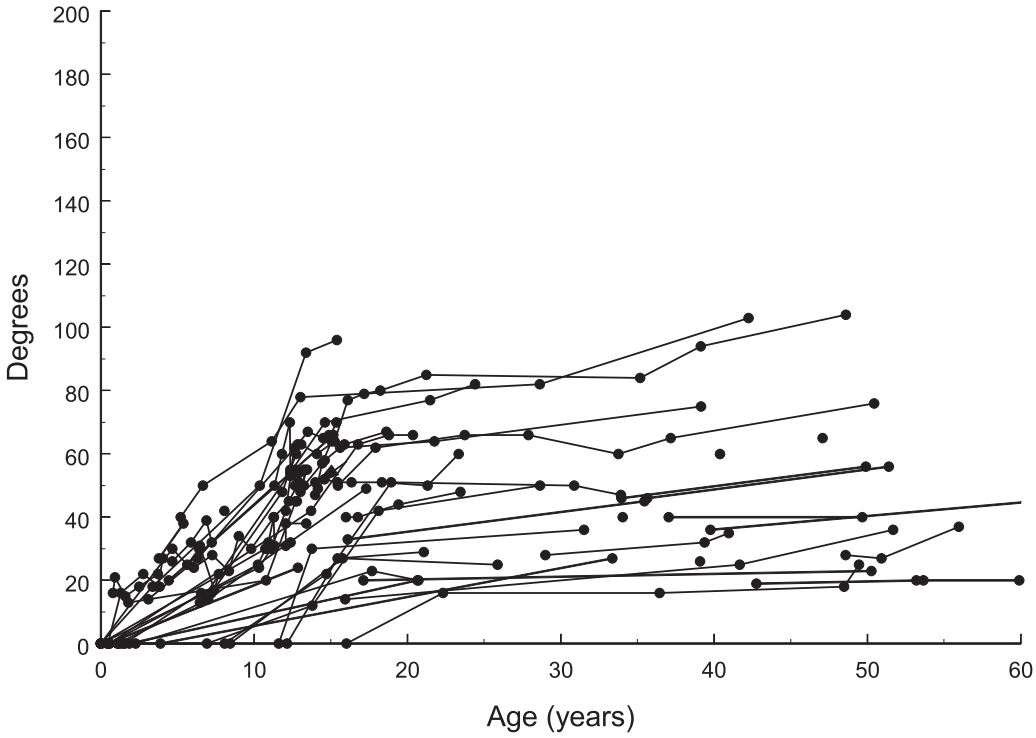

FIGURE 11. Natural history of idiopathic-like type of scoliosis from birth to 60 years. One circle is one radiograph.

Local curves associated with asymmetric disc degeneration (30 patients) (Figure 12) and local lumbar curve with pelvic tilting (six patients) were also noted. The curves were usually evident at adulthood, also in eight patients with follow-up radiographs from childhood (Figure 13). No significant progression (Figure 13) or rotation of the curves was seen during follow-up. All curves were over 10 degrees but only in one (3%) patient did the curve was exceed 30 degrees. The curves averaged 18 (range 11 – 40) degrees at the last radiograph. In the lateral view, sagittal deformities were uncommon and usually mild. In the thoracic spine, the average kyphosis was 24 (range 4 - 46) degrees and in the lumbar spine, the average lordosis was 31 (range 4 – 72) degrees. A triple (kyphosis-lordosis-kyphosis) curve pattern was seen in one patient and a quadruble curve pattern in five patients. In addition, long kyphosis from the upper thoracic spine to the lower lumbar spine was noted in one patient. The average lordosis in the lower thoracic spine was 11 (range 9 –14) degrees and kyphosis in the lumbar spine was 24 (range 4 – 60) degrees. Curves associated with

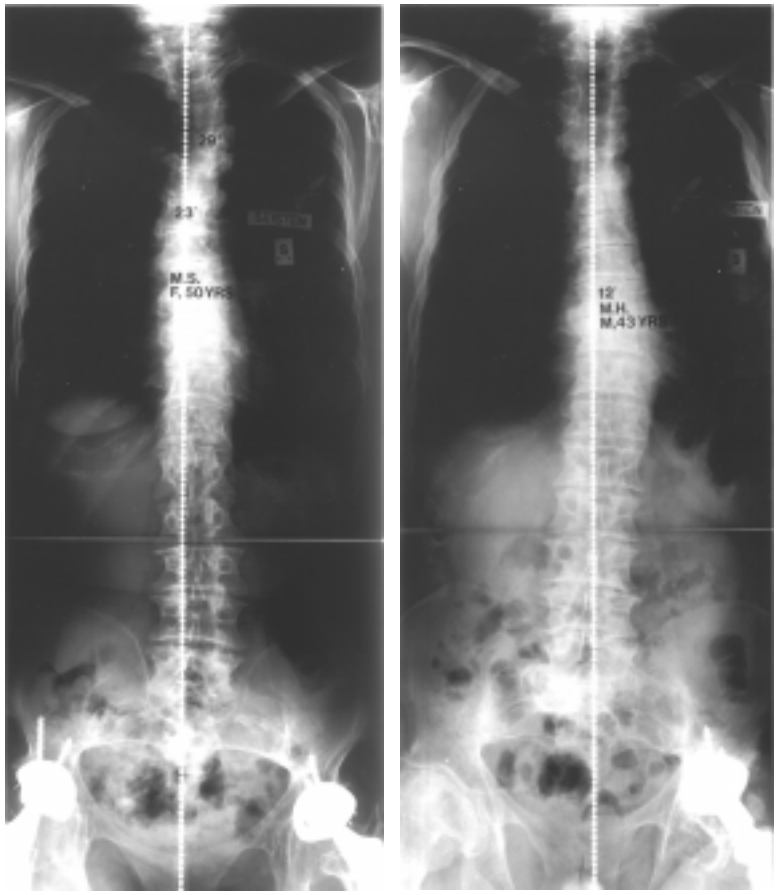

***FIGURE* 12a-b.** Two siblings with the mild, non-progressive type of scoliosis. Note the similar curve patterns and degenerative changes associated with this type.

disc degeneration were reminiscent of type XI in Coonrad's classification (Figure 12a-b).

Scoliosis could thus be divided into three subtypes: 1) early progressive, 2) idiopathic-like and 3) mild non-progressive (Table 4). The scoliosis of one patient was not compatible with this classification: he had congenital scoliosis due to a wedged vertebral body of L2 noted at the age of 1 year.

Intrafamilial variation in scoliosis

The early progressive type of scoliosis was seen in one pair of siblings; the idiopathic-like type in four and the mild, non-progressive type in three siblings (Table

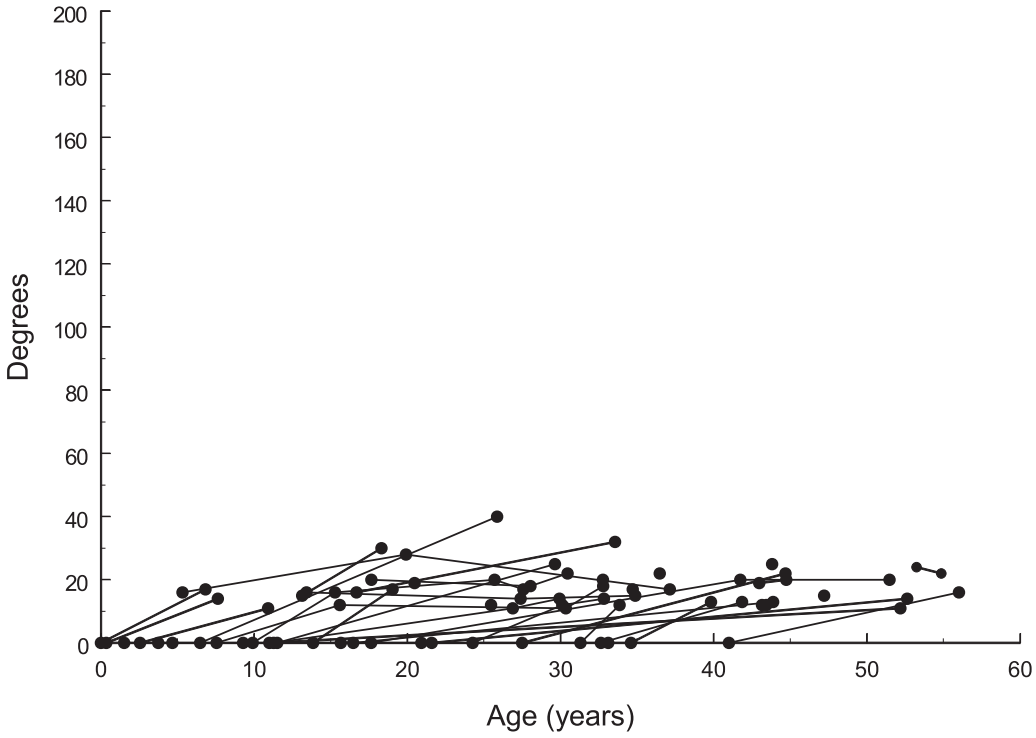

FIGURE 13. Natural history of mild non-progressive type of scoliosis from birth to 60 years. One circle is one radiograph.

5). In three families, patients had either the idiopathic-like or mild, non-progressive type of scoliosis. However, in two of these three families the patients had only a mild idiopathic-like or mild, non-progressive type of curve (Table 5); only in one family did one patient have a moderate idiopathic-like and the other patient a mild, non-progressive type of curve.

Feature / Subtype	Early progressive	Idiopathic-like	Mild non-progressive
Age of onset	< 3 years	< 10 years	> 15 years
Progression	Rapid	Mild to moderate	No
Curve pattern	Low thoracic or thoracolumbar	Similar to those of AIS	Multicurve or lumbar
Thoracic kyphosis or lordosis	Severe kyphosis	Mild lordosis - severe kyphosis	Mild lordosis - mild kyphosis
Rotation of vertebrae	+++	+ / ++	-
Magnitude of deformity at type end of growth, if untreated	> 100 degrees	> 30 degrees	< 30 degrees

TABLE 4. Typical features of different subtypes of scoliosis.

	Age	Apex	Convex	Magnitude	Type
Family 1					
F	34	Th	Right	188°	Early progressive
M	28	Th	Left	112°	Early progressive
Family 2					
M	50	L	Left	40°	Idiopathic-like
M	39	Th	Right	26°	Idiopathic-like
M	52	Th-L	Left	36°	Idiopathic-like
Family 3					
F	56	L	Left	37°	Idiopathic-like
F	63	Th-L	Left	35°	Idiopathic-like
Family 4					
F	29	Th	Left	91°	Idiopathic-like
F	24	Th	Right	82°	Idiopathic-like
Family 5					
F	21	Th	Left	20°	Idiopathic-like
F	32	Th-L	Left	36°	Idiopathic-like
Family 6					
F	43	L	Right	12°	Mild non-progressive
F	53	Th	Right	14°	Mild non-progressive
Family 7					
F	3	Th-L	Right	14°	Mild non-progressive
M	25	Th	Left	12°	Mild non-progressive
Family 8					
F	52	Th	Right	11°	Mild non-progressive
F	51	Th	Left	20°	Mild non-progressive
Family 9					
F	47	Th	Left	15°	Mild non-progressive
F	45	L	Left	20°	Mild non-progressive
F	50	Th	Right	23°	Idiopathic-like
Family 10					
M	33	L	Left	20°	Mild non-progressive
F	40	Th	Right	60°	Idiopathic-like
Family 11					
F	41	L	Left	35°	Idiopathic-like
F	30	L	Right	22°	Mild non-progressive
F	34	Th	Left	12°	Mild non-progressive

TABLE 5. Scoliosis in eleven families with siblings. M = male and F = female. Age = age at time of the last radiograph. Apex = primary curve thoracic (Th), thoracolumbar (Th-L) or lumbar (L), Magnitude = Magnitude of curve in degrees in the last radiograph. Type of curve according to our classification.

MRI data

Skull base

The signal intensity and the location of the medulla oblongata and cerebellar tonsils were normal. None of the patients had foramen magnum stenosis; on the contrary, the foramen magnum appeared to be wider than normal. Nor were there any patients with basilar invagination. In all of them, the tip of the dens in relation to Chamberlain's line was within normal limits (1 mm ±6.6 mm) [181].

Spinal cord and canal

In general, the spinal cord was normal. MRI showed normal signal intensity of the spinal cord in all patients (n=90) with no signs of medullar atrophy. Deformation of the medulla was often associated with cervical or thoracolumbar kyphosis. Two (16%) out of 12 patients in the age group 0 – 10 years had mid-cervical kyphosis. Their ages were 4 and 18 months and the magnitude of kyphosis was 90 and 40 degrees, respectively. The former patient subsequently died. One patient had an 165-degree kyphosis at the age of 32 years. Deformation of the medulla was related to the severity of the kyphosis (Figure 14a-b).

In patients with severe scoliosis, the medulla was located on the concave side of the curve in the spinal canal (Figure 15). One patient, a 30-year-old male, had a local syrinx at levels Th7 to Th9. Moreover, half of the patients, three (30%) aged 0 – 10 years, six (43%) aged 11 – 20, 17 (43%) aged 21 – 40 and 17 (71%) aged 41 – 60 years, had mild dilatation of the central canal. The conus was located at the level of the Th12 vertebra or of the intervertebral disc below it in five (6%) patients, at the level of L1 in 79 (93%) patients and at the level of L2 in one (1%) patient. This is within normal limits [168,218]. The location of the conus could not be defined in three patients due to imaging artefacts caused by the spinal instrumentation hardware.

The spinal canal was narrowed, but severe spinal stenosis was uncommon. Table 6 lists the results of the arbitrary scale grading of the spinal canal width. The most markedly narrowed levels were in the cervical and lumbar spine, especially at the levels of C3 to C6 and L3 to S1. Narrowness increased with age due to the progression of degenerative changes. However, only one patient, a 50-year-old male, had both thoracic and lumbar spinal stenosis (Figure 16). One patient in the age group

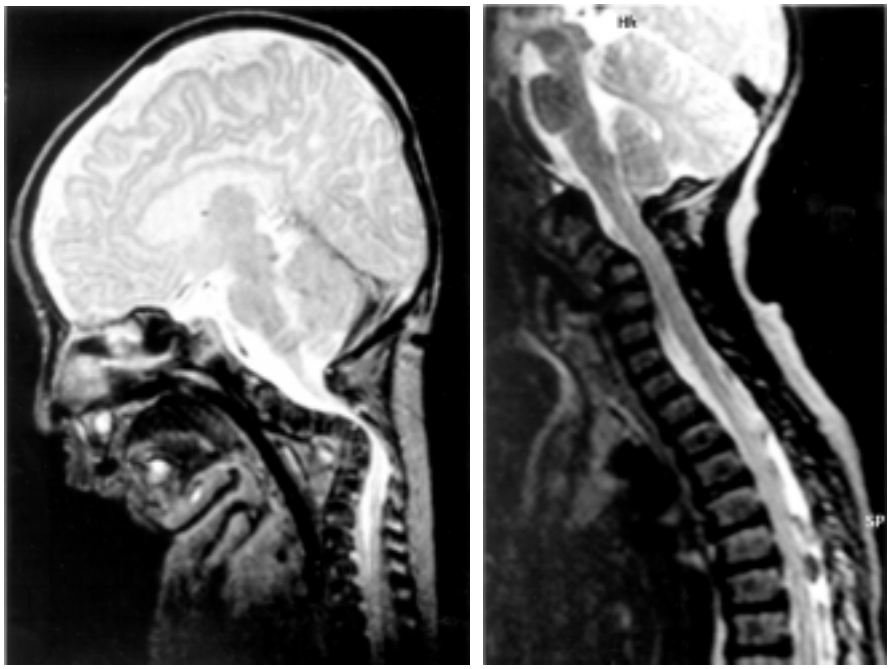

***FIGURE* 14a-b.** Sagittal T2-weighted image from three-month-old patient (a). Severe cervical kyphosis causes marked medullar compression. Despite of performed anteroposterior fusion and decompression, the patient died. Sagittal T2—weighted image from one year and seven months old patient (b). Mild kyphosis causes narrowing of the spinal canal, but not medullar compression. In the both patients cervical vertebrae and intervertebral discs are narrow and signal intensity of the discs is abnormally low.

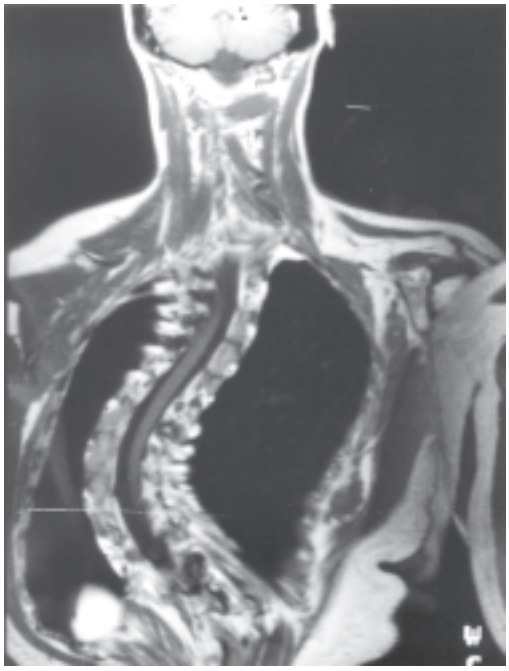

FIGURE 15. The T1-weighted magnetic resonance image of a 48-year-old female. Medulla is located on the concave side of the curve in the spinal canal.

	C1-5								C5-Th2							
	gr 1		gr 2		gr 3		gr 4		gr 1		gr 2		gr 3		gr 4	
Age group	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0 – 10	41	85	5	10	0	0	2	4	46	96	1	2	1	2	0	0
11 – 20	55	98	1	2	0	0	0	0	56	100	0	0	0	0	0	0
21 – 40	132	83	23	14	2	1	3	2	147	92	9	6	3	2	1	1
41 – 60	66	69	18	19	10	10	2	2	82	85	11	11	3	3	0	0
Total	294	82	47	13	12	3	7	2	331	92	21	6	7	2	1	0

	Th2-7								Th7-12							
	gr 1		gr 2		gr 3		gr 4		gr 1		gr 2		gr 3		gr 4	
Age group	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0 – 10	47	94	3	6	0	0	0	0	50	100	0	0	0	0	0	0
11 – 20	63	94	4	6	0	0	0	0	62	100	0	0	0	0	0	0
21 – 40	184	95	9	5	0	0	0	0	188	99	1	1	1	1	0	0
41 – 60	112	93	4	3	2	2	2	2	100	83	19	16	1	1	0	0
Total	406	94	20	5	2	0	2	0	400	95	20	5	2	0	0	0

	Th12-L3								L3-S1							
	gr 1		gr 2		gr 3		gr 4		gr 1		gr 2		gr 3		gr 4	
Age group	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0 – 10	29	97	1	3	0	0	0	0	25	83	5	17	0	0	0	0
11 – 20	33	87	5	13	0	0	0	0	30	71	8	19	4	10	0	0
21 – 40	100	88	9	8	4	4	0	0	76	68	26	23	9	8	1	1
41 – 60	50	69	18	25	1	1	3	4	35	51	26	38	7	10	1	1
Total	212	84	33	13	5	2	3	1	166	66	65	26	20	8	2	1

TABLE 6. Size of spinal canal from C1 to S1 evaluated on an arbitrary scale. Grades were 1) normal amount of cerebrospinal fluid (CSF) around medulla, 2) decrease in CSF around medulla, 3) no CSF around medulla, and 4) medullar compression n = number and % = percentage.

21 – 40 years and four patients in the age group 41 – 60 years had radiological signs of compression of neural structures in the lumbar spinal canal, but no clinical symptoms.

The average and standard deviation (SD) for transverse areas of the spinal cord in the cervical and in the lumbar and the dural tube are shown in Table 7. The transverse areas of the spinal cord and the dural tube were smaller in patients with DD

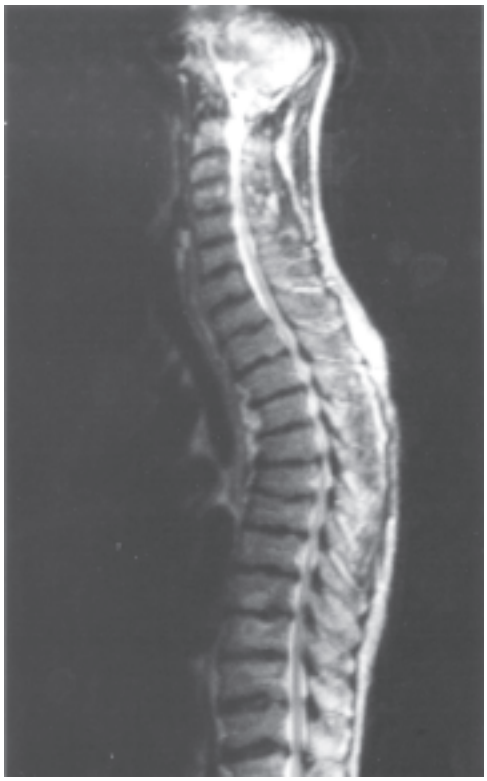

FIGURE 16. The magnetic resonance image of a 50-year-old male with severe spinal stenosis in the thoracic spine. Decompression and posterior spinal fusion with instrumentation were later performed on this patient.

than in healthy subjects ($p < 0.0001$), except in the spinal cord area at the level of intervertebral disc C6-7 ($p = 0.15$).

Intervertebral discs

The intervertebral discs were abnormal in all patients. The discs were either speckled or black on T2-weighted images (Table 8, Figure 17). The older the patients , the higher the frequency of black discs, and they were most often seen in the cervical and in the upper thoracic spine. The signal intensity from discs C2-6 and L2-S1 of patients aged 20 years or over was lower than that from asymptomatic individuals [20,126] ($p < 0.001$). There was no difference in the signal intensity from discs Th2-S1 either between adult patients with scoliosis and without scoliosis or between adult patients with scoliosis of less than 50 degrees and with scoliosis of over 50 degrees. The disc spaces, especially in the cervical and in the thoracic spine, were narrower than in the normal population in every age group.

In the cervical spine, 12/90 (13%) patients had 14 bulges and only 2/90 (2%) patients had a prolapse. In the thoracic spine, 39 (44%) of the 88 patients had a disc

	Spinal Cord (mm^2)			Dural Tube (mm^2)		
Level	AreaControl	AreaDD	Ratio	AreaControl	AreaDD	Ratio
C2-3	79.4 ± 6.9	66.0 ± 1.4	1.2	218.8 ± 31.4	172.6 ± 6.6	1.3
C3-4	82.9 ± 7.2	65.2 ± 1.4	1.2	192.6 ± 21.9	132.2 ± 4.5	1.5
C4-5	85.8 ± 7.2	69.9 ± 1.5	1.2	189.8 ± 20.3	136.3 ± 4.3	1.4
C5-6	81.2 ± 7.2	72.4 ± 1.4	1.1	186.0 ± 20.3	147.7 ± 4.4	1.3
C6-7	69.3 ± 8.0	66.7 ± 1.4	1.0	186.6 ± 22.0	150.7 ± 4.5	1.2
L2-3				170 ± 39	93.6 ± 36.4	1.8
L3-4				157 ±39	74.7 ± 31.0	2.1
L4-5				153 ±42	62.9 ± 29.2	2.4
L5-S1				129 ±55	56.9 ± 32.1	2.3

TABLE 7. Data on spinal cord and dural tube area. Reference data (areaControl) on healthy individuals from reports by Hamanishi et al. (J Spinal Disord 7:388-393, 1994) and Okada et al. (Spine 1994;19:2331-5.) were compared with data (areaDD) on patients with diastrophic dysplasia.

	C2-6				C6-Th2				Th2-7			
Age group	S	%	B	%	S	%	B	%	S	%	B	%
0 – 10	0	0	48	100	0	0	36	100	1	2	49	98
11 – 20	0	0	56	100	0	0	42	100	3	4	66	96
21 – 40	0	0	160	100	0	0	120	100	1	1	199	100
41 – 60	0	0	96	100	1	1	71	99	0	0	120	100
Total	0	0	360	100	1	0	269	100	5	1	434	99

	Th7-12				Th12-L3				L3-S1			
Age group	S	%	B	%	S	%	B	%	S	%	B	%
0 – 10	20	40	30	60	11	37	19	63	9	30	21	70
11 – 20	17	26	48	74	18	46	21	54	11	27	30	73
21 – 40	16	8	182	92	24	21	92	79	16	14	100	86
41 – 60	2	2	118	98	5	7	67	93	5	7	67	93
Total	55	13	378	87	58	23	199	77	41	16	218	84

TABLE 8. Results of grading signal intensity of intervertebral discs on T2-weighted images. S = number of speckled intervertebral discs. B = number of black intervertebral discs.% = f speckled or black discs as percentage of total number of discs. No intervertebral discs were classified as normal.

bulge at one level at least in the thoracic spine and one (1%) had a prolapse; numbers in the lumbar spine were 56 (64%) and 2 (2%), respectively. The frequency of disc bulges in the lumbar spine decreased with age (Table 9). In the cervical spine, the frequency of bulges lower than shown by the reference values [126] ($p < 0.0001$), but in the thoracic and in the lumbar spine frequency of bulges was same as in healthy subjects [88,221]. However, our patients had significantly fewer prolapses in the whole spine than did subjects in the normal population ($p < 0.001$).

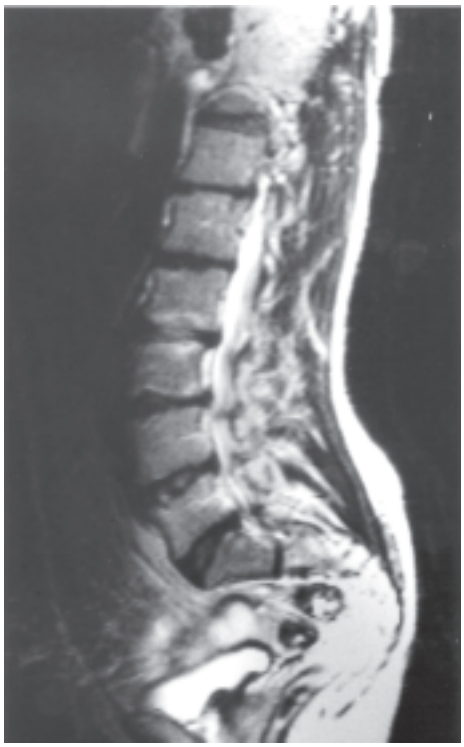

FIGURE 17. The T2-weighted magnetic resonance image of a 30-year-old male. Note the dark intervertebral discs, especially in the thoracic spine.

	C2-7				C7-Th2				Th2-7			
	Bulge		Prolapse		Bulge		Prolapse		Bulge		Prolapse	
Age group	n	%	n	%	n	%	n	%	n	%	n	%
0 – 10	1	2	0	0	1	4	0	0	1	2	0	0
11 – 20	0	0	0	0	0	0	0	0	5	7	1	1
21 – 40	7	4	0	0	7	9	0	0	14	7	0	0
41 – 60	6	5	1	1	7	15	1	1	5	4	0	0
Total	14	3	1	0	15	8	1	0	25	6	1	0

	Th7-12				Th12-L3				L3-S1			
	Bulge		Prolapse		Bulge		Prolapse		Bulge		Prolapse	
Age group	n	%	n	%	n	%	n	%	n	%	n	%
0 – 10	0	0	0	0	23	77	0	0	21	70	0	0
11 – 20	3	5	0	0	18	46	0	0	20	45	3	7
21 – 40	6	3	0	0	17	15	0	0	18	16	0	0
41 – 60	9	8	0	0	19	26	0	0	17	24	0	0
Total	18	4	0	0	77	30	0	0	76	29	3	1

TABLE 9. Number (n) and percentages (%) of bulges and prolapses at different levels of the cervical, thoracic and lumbar spine. A bulge was defined as a small, diffuse, non-focal protrusion of non-osseous disc material and a prolapse as a focal extrusion.

Vertebrae

In the MR images, three (3%) of the 90 patients had cervical and one (1%) of 88 had thoracolumbar kyphosis. In the radiographs, scoliosis was noted in 70 (80%) of the 88 patients with MR images with an average of 42 (range 11 – 188) degrees.

Dens was normal in the age group 0 – 10 years in all patients. A hypertrophied dens was noted in the age groups 11 – 20, 21 – 40 and 41 – 60 years, with four (29%), 14 (35%) and 11 (46%) patients in each group, respectively. The rest of the patients in the age groups had a normal dens. Medullar deformation due to the hypertrophied dens was noted as follows: one (9%) in the 0 – 10, three (21%) in the 11 – 20, six (15%) in the 21 – 40 and three (13%) patients in the 41 – 60 year age groups (Figure 18).

Vertebral hypoplasia from C3 to C5 was associated with kyphosis. On the other hand, in adult patients with cervical lordosis the sagittal diameter of the four-cornered vertebral bodies from C3 to C5 seemed to be increased. Only two patients had vertebral anomalies: a 17-year-old female had a Th7 butterfly vertebra and a

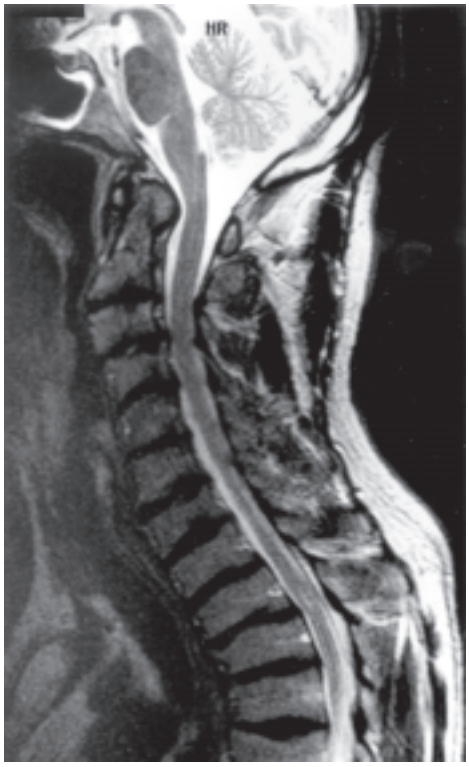

FIGURE 18. The cervical spine was always abnormal. Typically, vertebral bodies and intervertebral discs are narrow and signal from discs is low and foramen magnum is exceptionally wide. Degenerative changes with end-plate irregularities and ”hypertrophied” dens in 39-year-old male patient. Spinal canal was also narrowed.

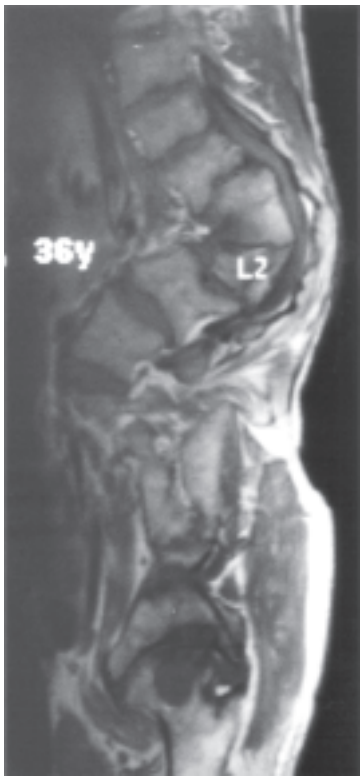

FIGURE 19. The T1-weighted magnetic resonance image of a 36-year-old male. Junctional thoracolumbar kyphosis caused compression of neural structures.

34-year-old male had an L2 anteriorly wedged vertebra (Figure 19).

Spondylotic bone spurs in the anterior and posterior margins of the vertebrae could already be observed in the age group 11 – 20 years and their prevalence increased with age. These degenerative changes affected all adult patients. All patients exhibited degenerative-like hypertrophy of the facet joints in the lumbar spine (Figure 20), and severity seemed to increase as the patients aged. One patient, a 24-year-old male, had L 5 spondylolysis and -olisthesis.

Schmorl node's prevalence was stable after adolescence (Table 10). Of the 88 patients with MR images of the cervical spine to the sacrum, 43 (49%) had at least one Schmorl's node. In the cervical spine Schmorl's nodes were seen in two (5%) and five (21%) patients in the age groups 21 – 40 and 41 – 60 years, respectively. In the thoracic spine, one (10%) patient in the 0 – 10 , six

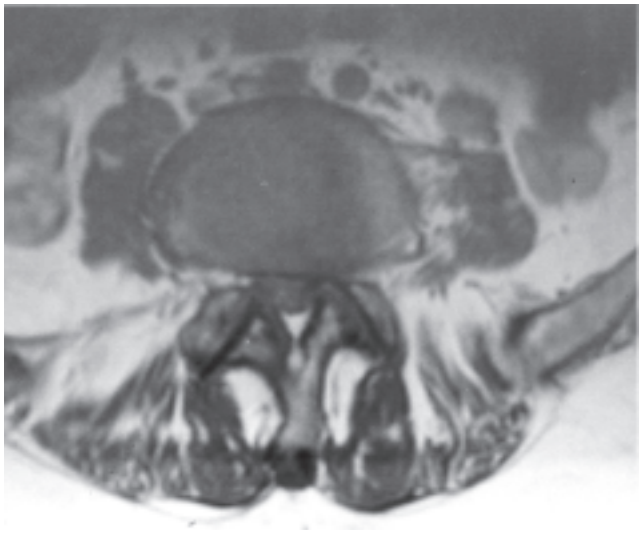

FIGURE 20. The T1-weighted magnetic resonance image of a 45-year-old female. As well as hypertrophied facet joints, there is severe muscle atrophy.

	C2-6						C6-Th2					
	SN		Type I		Type II		SN		Type I		Type II	
Age group	n	%	n	%	n	%	n	%	n	%	n	%
0 – 10	0	0	0	0	0	0	0	0	0	0	0	0
11 – 20	0	0	0	0	0	0	0	0	0	0	0	0
21 – 40	5	3	1	1	1	1	4	3	0	0	0	0
41 – 60	5	5	0	0	0	0	4	4	0	0	0	0
Total	10	3	1	0	1	0	8	2	0	0	0	0

	Th2-7						Th7-12					
	SN		Type I		Type II		SN		Type I		Type II	
Age group	n	%	n	%	n	%	n	%	n	%	n	%
0 – 10	0	0	0	0	0	0	0	0	0	0	0	0
11 – 20	3	4	0	0	0	0	11	18	1	2	0	0
21 – 40	14	7	1	1	0	0	20	10	4	2	0	0
41 – 60	13	11	0	0	2	2	16	13	5	4	5	4
Total	30	7	1	0	2	0	47	11	10	2	5	1

	Th12-L3						L3-S1					
	SN		Type I		Type II		SN		Type I		Type II	
Age group	n	%	n	%	n	%	n	%	n	%	n	%
0 – 10	3	10	1	3	0	0	3	10	0	0	0	0
11 – 20	7	18	2	5	0	0	5	12	0	0	1	2
21 – 40	10	8	2	2	8	7	3	3	3	3	13	11
41 – 60	9	13	6	8	5	7	4	6	2	3	4	6
Total	29	11	11	4	13	5	15	6	5	2	18	7

TABLE 10. Number (n) and percentage (%) of Schmorl's nodes (SN), and type I and II bone marrow changes in studied vertebrae of the thoracic and lumbar spine. Schmorl's nodes, defined as herniation of disc into the vertebral body end-plate, and bone marrow changes were also noted. Bone marrow changes were classified as type I, defined as decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images, or type II, defined as increased signal intensity on T1-weighted images and isointense or slightly increased signal intensity on T2-weighted images.

(43%) in the 11 – 20, 18 (45%) in the 21 – 40 and nine (38%) in the 41 – 60 year age groups had Schmorl's nodes. In the lumbar spine, the numbers for these age groups were four (40%), six (43%), four (10%) and eight (33%), respectively. Table 10 gives the number and percentage of Schmorl's nodes in the studied vertebrae. In statistical comparison with healthy subjects [88,221] we found no difference in patients aged 20 years or over in the thoracic or in the lumbar spine.

In our study, bone marrow changes were usually seen in the lumbar spine of the adult patients. Type I bone marrow changes were found in one (1%), nine (10%) and 13 (15%) patients in the cervical, in the thoracic and in the lumbar spine, respectively. The numbers for type II bone marrow changes were one (1%), six (7%) and 21 (24%), respectively.

Muscles

Muscular atrophy was common. The psoas muscles in 99% and the back muscles in 92% of the patients were considered abnormal by visual assessment of T1-weighted MR images (Table 11, Figure 21). The older the patient the more severe was the observed atrophy. Back muscles contained high signal intensity fatty streaks within the muscle mass. The atrophied psoas muscles showed a diminished cross-section area, but fat was not detected within the muscle. The patients with the most fatty streaks and the smallest back muscles also had the most atrophied psoas muscles, too. We found a highly significant difference ($p < 0.001$) in the prevalence of muscular atrophy between adult patients and the normal, healthy population [142]. There was no difference in the prevalence of the muscle abnormality either between adult patients with scoliosis and without scoliosis or between adult patients with scoliosis of less than 50 degrees and with scoliosis over 50 degrees.

	Iliopsoas muscles						Paraspinal muscles					
	Normal		Mild		Severe		Normal		Mild		Severe	
Age group	n	%	n	%	n	%	n	%	n	%	n	%
0 – 10	0	0	10	10	0	0	4	40	6	60	0	0
11 – 20	0	0	10	71	4	29	1	7	9	64	4	29
21 – 40	1	3	13	34	24	63	2	5	17	46	18	49
41 – 60	0	0	8	33	16	67	0	0	9	38	15	63
Total	1	1	41	48	44	51	7	8	41	48	37	44

TABLE 11. Results of visual assessment of psoas and back muscles in different age groups. Muscle status was estimated on an arbitrary scale with three grades: 1) normal, 2) mild atrophy and 3) severe atrophy. The back muscles, that is, the erector spinae and multifidus, were estimated together. n = number and % = percentage.

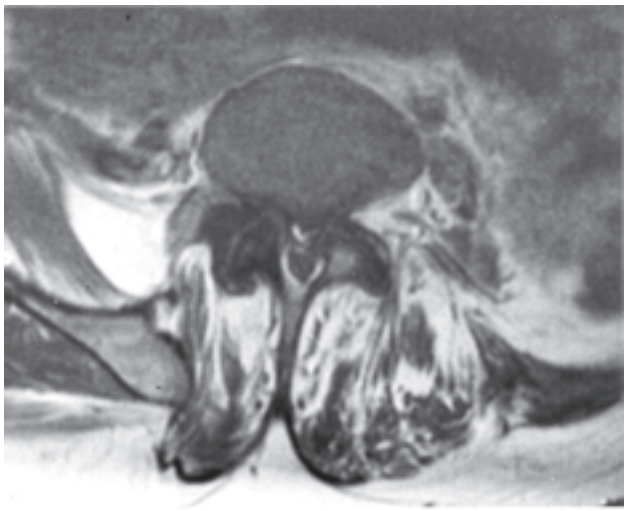

FIGURE 21. The T1-weighted magnetic resonance image on the right was taken of a 35-year-old female. Note the severe atrophy in the paraspinal and iliopsoas muscles.

DISCUSSION

Material and methods

The patient population in this study was unselected and included those with only a mild clinical picture. The data on one sample may therefore be interpreted and transformed to represent the patient population. The prevalence of DD is higher in Finland than reported elsewhere [93], and the fact that the number of Finnish patients with DD accounts for about half of the known patient population worldwide enabled the spinal deformities to be investigated in detail.

In the radiographical studies (I and III) there was a follow-up of the majority of the patients with spinal deformity. However, the interval between the spinal radiographs varied due to the nature of the studies (partly retrospective). MRI is an excellent tool in evaluation of the soft tissues, the contents of the spinal canal in particular. However, Myelo-CT is better than MRI at demonstrating spinal stenosis caused by bony structures [18,107] and it can be a complementary investigation in evaluation of spinal stenosis. Disadvantages of myelo-CT are invasiveness and radiation. MR studies were cross-sectional and follow-up MR images would have offered more close evaluation.

In measurement of the scoliotic angle from plain radiographs, the mean inter- and intraobserver error has been small, ranging from 1.5 to 4.2 degrees [12,49,59,134,136,174,223].

Findings on MR images were compared, if possible, with those reported on healthy subjects [19,88,126,133,141]. There was no difference in sex distribution between our patients and those in reference groups. However, our patients tend to be younger (4 to 10 years). This difference was statistically significant, except in one case, but not necessarily clinically significant. Evaluation of the findings is based on visual assessment rather than on absolute measurements. Measurements from MR images were compared with reference values reported elsewhere [65,139]. However, these reports were from a Japanese population; none were available on a Caucasian population at the time of the study. Hultman et al. [83] and Karantanas et al. [97] found a correlation between the transverse area of the spinal canal and a person's body length. The Japanese are shorter than Caucasians [140,195] and so the reference values used may be lower than those from a Caucasian population. The literature gives no reference values for children and the thoracic spine.

Physical examination

The impaired mobility of the spine found on physical examination is attributed to abnormal intervertebral disc structure and rapid degeneration, rigid ligamentous structures and the high prevalence of spinal deformities. Physical examination included, in addition of those reported on methods section, measurement of standing height, sitting height and weight. Movement of the hip and knee joints, stability of the knee joint and deformity of the feet were evaluated. Patellar and achilles reflexes and sense of the skin in the L4-S1 dermatomes were also studied. Results of these studies will be reported elsewhere. Laseque's test is not reliable in patients with DD is due to diminished range of movements in the hip and knee joints.

Cervical kyphosis

Cervical kyphosis is usually shown in childhood. The majority of DD patients with cervical kyphosis in our study, as reported also in the literature, were young [2,17,28,73,100,105,106,116,156,214]. In our study, 66 patients had no radiographs from early childhood, but it is possible that these adult and adolescent patients with normal lordosis had a kyphotic deformity as children. The swan-neck deformity noted in two patients may be a result of an incompletely resolved kyphosis or degeneration.

Cervical kyphosis usually resolves spontaneously. The clinical and radiological outcome of cervical kyphosis in DD differs from other skeletal dysplasias. Spontaneous resolution of this deformity is not seen in patients with Larsen's syndrome or camptomelic dysplasia [23,44,53,90].

Living adult patients with DD and severe cervical deformity are rare. The kyphosis remained unresolved during follow-up in two living patients. The first patient had an 165-degree kyphosis at the age of 32 years and had no major neurological complications. There were no problems with anaesthesia in her previous foot operations between ages of 6 to 12 years. For the second patient, a 4-year-old child with a 10-degree kyphosis at the last follow-up, spontaneous resolution is to be expected during the next few years.

Cervical kyphosis was associated to increased mortality in this series. Three patients with severe kyphosis died. Two of them, both new-borns, had severe tracheo- and bronchomalasia, and their deaths were most likely due to severe kyphosis with

POSTURAL AND ANATOMICAL FACTORS	DEVELOPMENTAL FACTORS
- Cervical spine of foetus in utero is in hyperflexion	- Hypoplastic and defectively ossified vertebrae in cervical spine
- The increased angle of facet joints allows more movement between vertebrae in AP direction (phenomenon is also known as pseudodislocation or -luxation.)	· Hypoplastic vertebrae can be seen in radiographs of new-borns with DD
	· Vertebral ossification begins from lower cervical vertebrae and proceeds upwards, C1 and C2 ossify in differently from other cervical vertebrae ⇒ mid-cervical vertebrae are the last to ossify[138]
	· Ossification is delayed in DD⇒ mid-cervical vertebrae are usually hypoplastic
	· Severe hypoplasia in C3 or C4 causes wedge-shaped form of vertebral body, which together with posterior position of vertebra, increases the angle of kyphosis
	- Abnormal ligament structures

TABLE 12. Factors which may be related to the formation of cervical kyphosis in DD in utero.

myelopathy combined with severe tracheo- and bronchomalasia. The third patient became quadriplegic during anaesthesia, possibly due to extension of the cervical spine during intubation. He had shown no major neurological symptoms before surgery. Severe forms of kyphosis causing medullar compression leading to quadriplegia and death have also been reported in the literature [28,100,152].

The pathogenic mechanism of kyphosis is unknown. This deformity most likely develops in utero, because it is already evident at the neonatal age. Tables 12 and 13 set out factors which could be linked to the formation and resolution or progression of this deformity. Vertebral hypoplasia is probably due to delayed and/or defective growth of the cartilaginous structures. The anterior part of the vertebra is most severely affected, causing a wedge-shaped vertebral body and “bending” of the cervical spine. Posterior displacement of the apex vertebra is often associated with hypoplasia. No correlation has been found between the presence of spina bifida occulta and cervical kyphosis [17].

Severe kyphosis will usually progress. Kyphosis exceeding 60 degrees may progress due to biomechanical factors. On the other hand, Bethem et al. [17] reported on a

RESOLVING KYPHOSIS (<60°)	PROGRESSIVE KYPHOSIS (>60°)
- Child begins to hold the head up, which strengthens extensor muscles of cervical spine	- Highly hypoplastic C3 or C4 vertebrae, which causes marked wedge-shaped vertebrae
- Hypoplastic vertebrae become more normal	- Increased angle of kyphosis causes pathological load to the cartilaginous parts in vertebrae and to the ligaments ⇒ increase of mechanical stress impairs growth of vertebrae to “normal” four-cornered shape ⇒ angle of kyphosis increases
- Angle of facet joint is reduced, leading to decreased movement between vertebrae in AP direction	
- Angle of kyphosis is reduced and thus pathological load to the cartilaginous parts in vertebrae and to the ligaments is diminished ⇒ decrease of mechanical stress facilitates growth of vertebrae to “normal” four-cornered shape ⇒ angle of kyphosis decreases	- Progression leads to extensor-flexor muscle imbalance and thus extensor muscles may become flexor muscles

TABLE 13. Factors which may be related to the progression or resolution of cervical kyphosis in DD in childhood.

patient with a spontaneously resolved 82-degree kyphosis. In our patients, severe kyphosis was associated with the apex vertebra, which was round or triangular and posteriorly displaced. The same phenomenon has been reported elsewhere [2,17,28,73,100,105,106,214]. If the kyphosis is spontaneously resolved, the vertebral body of the apex develops into a more normal “four-cornered” shape and posterior displacement is reduced.

Severe kyphosis causes an abnormal atlantoaxial joint. On the basis of our data and other reports [2,17,28,53,73,100,106,214] severe kyphosis causes the position of the dens to become parallel to the occiput. Normal articulation between the upper cervical vertebrae is then impossible. Richards described one diastrophic patient with atlantoaxial instability [156]. We found no such instability in our study.

It is unclear, how useful conservative treatment is in preventing the progression of kyphosis. Bethem et al. described two patients with cervical kyphosis of 42 and 40 degrees who were placed in a Milwaukee brace for associated scoliosis [17]. The kyphosis resolved within 18 months in both patients, most likely reflecting the natural history of kyphosis rather than the effect of the treatment itself. Their most severe case, a patient with an 82-degree kyphosis, was not treated and had continual slow, spontaneous resolution [17].

Indications for operative treatment have not been established. Patients with severe

cervical deformity and medullar compromise are rare. In the literature, combined anterior and posterior fusion has been the most favoured technique [17,53,73,106]. However, such operations have been occasional with only a short follow-up and thus final conclusions cannot be drawn.

Scoliosis

An almost constant finding in the thoracic and the lumbar spine is scoliosis. The prevalence of scoliosis in this study was even higher than reported previously [152,205,215]. The high prevalence is not explained by diagnostic criteria, as the diagnosis of DD can be made without the presence of spinal deformity - although it is often present. In some patients early progressive type scoliosis can already be seen at the age of 3 years, but the prevalence is highest in adulthood, when mild forms of scoliosis can also be noted.

Three new subtypes of scoliosis were identified. The early progressive type can be distinguished from the idiopathic-like type on the basis of (1) curve type (Figures 8a-d and 10a-c), (2) age at onset, (3) rate of progression and (4) degree of rotation of curve. Patients with the early progressive type had the most severe outcome (Table 2). The mild non-progressive type of scoliosis is also readily distinguished. Only the lumbar curve associated with pelvic tilting and the single lumbar curve pattern (Coonrad's type 7) resembled each other. Discrimination is facilitated by the absence of both rotation and progression in radiographs.

The early progressive type is reminiscent of the progressive form of infantile idiopathic scoliosis, both having early onset, rapid progression and severe outcome [86,130]. In addition, patients have a shortened trunk and humpback appearance due to the combination of vertebral rotation and kyphosis in the upper thoracic region [87], as seen in our patients, too.

The curve patterns in the idiopathic-like type of scoliosis were similar to those seen in patients with adolescent idiopathic scoliosis (AIS). The curves were categorised according to King's and Coonrad's classifications. Fifteen patients (29%) with the idiopathic-like type of curve did not fit King's classification, which cannot accommodate single thoracolumbar, double thoracic or thoracolumbar, single lumbar, triple and multiple curve patterns. All curves could, however, be classified according to

Coonrad's classification. Hence Coonrad's classification, although originally introduced for the classification of idiopathic scoliosis, may be more appropriate for scoliosis in skeletal dysplasias. Nevertheless, both classifications play a only minor role in the planning of treatment, whether surgical or conservative, of patients with DD.

The pathogenic mechanism of scoliosis is not known. Asymmetric disc degeneration is associated with mild, local curves (Figure 12a-b). DD is caused by mutations in the DTDST gene, which encodes a certain sulphate transporter. Impaired function of the transporter leads to undersulphation of the proteoglycans [68] resulting in abnormal growth of cartilaginous structures [82,172,175] and of ligaments and tendons. The structure of the intervertebral discs is abnormal [53] and ligaments and tendons are often rigid. These changes may lead to imbalance in growth of the spine and the spinal deformity. Tolo et al. have stated that 40% of the patients had deformities due to segmental defect in the thoracolumbar spine [205]. In our study, only one patient had a vertebral anomaly of L2 causing scoliosis and thoracolumbar kyphosis.

The correlation between genotype and spinal deformities is unclear. Although clinical variability is known among siblings in patients with DD [79], the siblings in our study all showed a strong tendency to have similar spinal deformities (Figure 12a-b). Over 20 different mutations in the DTDST gene [68,191] have been described. It is possible that a different mutation or mutations lead to more severe spinal deformity. Additional studies incorporating knowledge of gene mutations in DD and the natural history of spinal deformities are needed.

Previously, the spinal deformities of patients with DD have been treated mainly with a conservative approach [16,73,104,127,152]. Severe scoliosis can cause imbalance of the trunk, leading to difficulties in gait and a reduction in the already short standing height [104,127,152]. Many of these patients had been allowed to develop severe deformities under the mistaken belief that surgery was inadvisable because of their young age and dwarf status [127]. In Finland, before the 1970s, the main interest focused on other orthopaedic problems, mainly those of the lower extremities [152]. Early surgical intervention has now been proposed by several authors [17,73,76,104,127,152,204,206,207]. The results of brace treatment for scoliosis have been poor [16,73,104,152] and currently bracing is not recommended in the treatment of patients with DD [152].

The indications for treatment of scoliosis in DD have not been established. From our results and those of previous studies [73,104,127,152,187,219], the most important prognostic factors of the progression are time of onset - the earlier the time of onset, the more rapid and severe the progression and curve type. It would seem that scoliosis of the early progressive type will always develop into a severe deformity unless surgery is performed. Both posterior fusion [73,104] and combined anterior and posterior fusion [127,152] have been proposed in the treatment of progressive curves.

Anteroposterior fusion is the treatment of choice in patients with the early progressive type scoliosis. The operation causes loss of the growth potential of the spine, but does not necessarily affect standing height [127]. On the other hand, there is apparently no growth spurt in patients with DD [128]. Timing of the surgery is important and we propose that it should be considered before the curve exceeds 70 degrees, which tends to be quite early.

The treatment of choice in patients with the idiopathic-like type of scoliosis is posterior fusion. Progression of the curve is slower and the operation can be performed later in life than in the early progressive type. We propose that surgery should be considered if the curve exceeds 50 degrees.

Patients with the mild non-progressive type of scoliosis do not apparently need treatment for their scoliosis.

Spinal cord and canal

Sagittal, but not coronal, deformities cause deformation of the medulla, and the foramen magnum tends to be wide. Severe kyphosis causes medullar compression [17,53,73,100,106,152], as was also shown in our two patients with cervical kyphosis and one patient with thoracolumbar gibbus. However, even in patients with the most severe kyphosis, the T2-signal intensity of the spinal cord was not increased. This may be due to slow progression of kyphosis and medullar compression, but could also be due to plasticity of the medulla in early childhood.

The spinal canal is developmentally narrowed. The ratio of the dural tube area (reference / DD) was greater than the ratio of the spinal cord area (reference / DD) in the cervical spine (Table 7). Thus the dural tube area is relatively even smaller than the

spinal cord area, suggesting that the spinal canal fails to reach its “normal” size during growth. Degeneration causes further narrowness in the spinal canal; the most narrowed levels are usually in the cervical (C3-6) or in the lumbar (L3-S1) area. However, in the cervical spine the narrowness was mainly due to large vertebral bodies constricting the spinal canal and to disc degeneration with osteophytes. In the lumbar spine, hypertrophy of the facet joints as well as disc degeneration caused increased narrowness. Poussa et al. [152] also noted a tendency towards narrowing of the interpedicular distances from L1 to L5. The advantage of arbitrary scaling is that it describes the degree of true narrowness better than absolute values.

Developmental narrowness of the spinal canal was accentuated by disc degeneration, notably in older age groups, and degenerative-like hypertrophy of the facet joints. Radiological signs of severe lumbar spinal stenosis were, however, uncommon. On the other hand, images were taken while the patients were in supine; in a standing position, pressure in the spinal canal is elevated [66] and extension of the lumbar spine increases, leading to a decrease in spinal volume [84,224]. Reports on the operative treatment of lumbar spinal stenosis are sparse: Kopits [104] discussed one patient and Poussa et al. two patients who needed decompressive procedures to relieve symptoms. Thus, it seems that despite the narrowed spinal canal, patients seldom need surgical treatment for spinal stenosis.

Despite the high prevalence of spinal deformities and the shorter trunk, the location of the conus in our series was normal. The conus is normally located between Th12 and L3 [168,218]. The effect of disturbed growth in patients with DD is most severe in the extremities, but the spine is also involved. The location of the conus in our patients was similar to that in the normal population, i.e. our patients have an absolutely, but not a relatively, shorter spinal cord. It is possible that longitudinal growth of the neural structures is partially regulated by growth of the axial skeleton, i.e. traction.

Intervertebral discs

Intervertebral discs develop abnormally. In all patients, the T2-signal of the disc was attenuated. The loss of the T2-signal in all discs studied may reflect disc degeneration. On the other hand, even the youngest child participating in our study had speckled or black discs. Moreover, as the structure of proteoglycans changes in patients with DD, their function, i.e. water binding capacity [30], also changes. Loss of water, i.e.

loss of protons, results in loss of signal on T2-weighted MRI images [202]. The loss of disc T2-signal intensity and height is therefore probably not solely due to degeneration; more likely discs fail to reach their normal water content and height during growth due to the presence of abnormal proteoglycans. The prevalence of prolapses was significantly lower in our patients with DD than in the normal population. One explanation might be that as the discs fail to reach their normal size and volume there is less material to protrude. The decrease noted in the number of bulges with age might be due to profound osteophytes.

Vertebrae

The prevalence of hypertrophied, large dens increased with age. The pathophysiology of the hypertrophy is unknown. In some patients, a hypertrophied dens also seemed to cause medullar deformation.

Hypoplasia of vertebrae C3-C5 was associated with cervical kyphosis. In the older age groups (21 years or over) the depth of these same vertebral bodies was often increased, as noted elsewhere [99]. Vertebral growth depends on both genetic and mechanical factors. Vertebral body height may even be primarily genetically determined [138,199], but horizontal growth and peripheral vertebral growth are more dependent on mechanical factors and upright posture [138,199]. It is possible that the overgrowth is a results of increased strain on these vertebrae due to kyphosis in childhood.

Vertebral anomalies were rare. Tolo et al. [205] found that 40% of patients with DD had deformities due to a segmental defect in the thoracic spine. In our study, only one patient had a vertebral anomaly of L2 causing scoliosis and thoracolumbar kyphosis; one other patient had a Th7 butterfly vertebra.

All patients had abnormal facet joints. The high prevalence of degenerative-like changes (hypertrophy) must be due, at least in part, to abnormal development of the cartilage facet joints. Hypertrophy increases with age due to the high frequency of disc degeneration, which causes changes to the mechanical loading of facet joints [33].

The prevalence and distribution of Schmorl's nodes were within normal limits in the thoracic and the lumbar spine. Reference values for the cervical spine were not available. Previous studies have associated an increase in degenerative changes with Schmorl's nodes [75,221]. Hilton et al. [75] found that Schmorl's nodes most often occur in the lower thoracic or the upper lumbar spine. In their study, the frequency of nodes did not increase after adolescence. Similar findings were made in our patients, although early degenerative changes were common in our study.

The prevalence of bone marrow changes was low. Modic type I bone marrow changes may be considered an acute or subacute response of the vertebral bone marrow to disc degeneration. In contrast, Modic type II changes reflect a more stable end state of the degeneration process [133]. An association has been reported between Modic type I bone marrow and LBP [208], but not with discography [25] or segmental instability of the lumbar spine [26]. The prevalence of these changes in the healthy population is not known.

Muscles

Atrophy of low back muscles was common. Atrophy may be due partly to diminished physical activity and partly to immobilisation caused by rigid deformities of the spine. The back muscles accumulated fat deposits whereas the psoas muscles did not (Figure 21). Parkkola et al. noted the same phenomenon [141,142] in healthy individuals. They also showed that neither the body-mass index (BMI) nor obesity has any correlation with the fat deposits of the back muscles. The severity of muscular atrophy increased with age in our patients. However, both the psoas and back muscles become smaller in old age in healthy individuals, too [141]. It is not known whether the histological and biochemical structure of muscles is normal in patients with DD.

CONCLUSIONS

From the results following conclusions can be made:

- Cervical kyphosis in DD is usually evident at birth. Prevalence of the deformity in childhood is high (96%). It almost always resolves spontaneously during growth by the age of 5 to 6 and seldom needs treatment. Signs of poor prognosis are an angle exceeding 60 degrees and round or triangular and posteriorly displaced apex vertebra.
- The exact pathogenic mechanism of kyphosis remains unknown. An abnormal intervertebral disc structure may be one aetiological factor. However, vertebral body hypoplasia seems to play a major role.
- Prevalence of scoliosis is high (77%) in patients with DD. Three different subtypes can be identified - early progressive, idiopathic-like and mild non-progressive. The natural history of scoliosis in patients with DD ranges from severe deformity and rapid progression (early progressive) to mild deformity without progression (mild non-progressive). The earlier the curve was initiated the more severe was its progression. The classification we propose may help to predict the natural history of scoliosis in DD and adjust the timing of surgery in individual patients.
- The exact pathogenic mechanism of scoliosis remained unclear. The abnormal intervertebral disc structure and the rigid ligamentous structures may be aetiological factors. In this respect; abnormal atrophied psoas and back muscles may be secondary changes. However, vertebral anomalies are not the aetiology of scoliosis as was previously suggested.
- The impaired mobility of the spine found on physical examination was attributed to abnormal intervertebral disc structure and height in addition to a high prevalence of spinal deformities.
- Abnormal MR findings on the spine in patients with DD are common. Intervertebral discs are developmentally abnormal and degeneration proceeds rapidly. Diastrophic dysplasia offers an interesting model of early disc degeneration caused by abnormal proteoglycan synthesis. Sagittal deformities cause deformation of the medulla. The spinal canal area is narrowed, but absolute lumbar spinal stenosis is uncommon.
- In forthcoming studies we shall focus on incorporating knowledge of gene mutations in DD and the natural history of scoliosis in order to establishing whether genotype can be used to predict of the severity of scoliosis.

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“It’s only with the heart that one can see rightly; what is essential is invisible to the eye.”

The Little Prince - Antoine de Saint Exupéry

Helsinki, May 2000

REFERENCES

1. ***Acheson MB, Livingston RR, Richardson ML, Stimac GK.*** High-resolution CT scanning in the evaluation of cervical spine fractures: comparison with plain film examinations. Am J Roentgenol 148:1179-1185, 1987.
2. ***Amuso SJ.*** Diastrophic dwarfism. J Bone Joint Surg (Am) 50:113-122, 1968.
3. ***Angtuaco EJ, Binet EF.*** Radiology of thoracic and lumbar fractures. Clin Orthop 189:43-57, 1984.
4. ***Apajasalo M, Sintonen H, Rautonen J, Kaitila I.*** Health-related quality of life of patients with genetic skeletal dysplasias. Eur J Pediatr 157:114-121, 1998.
5. ***Armstrong GW, Livermore NB, 3d, Suzuki N, Armstrong JG.*** Nonstandard vertebral rotation in scoliosis screening patients. Its prevalence and relation to the clinical deformity. Spine 7:50-54, 1982.
6. ***Bailey JA.*** Disproportionate Short Stature. Diagnosis and Management. WB Saunders, Philadelphia, 1973.
7. ***Bassett GS.*** Lower-extremity abnormalities in dwarfing conditions. Instr Course Lect 39:389-397, 1990.
8. ***Bassett GS.*** Orthopaedic aspects of skeletal dysplasias. Instr Course Lect 39:381-387, 1990.
9. ***Bassett GS, Scott CI, Jr.*** The Osteochondrodysplasias. In Morrissy RT (ed). Lovell's and Winter's Pediatric Orthopedics. pp. 91-138, Halliday Lithograp, 1990.
10. ***Bassett LW, Gold RH.*** Magnetic resonance imaging of the musculoskeletal system. An overview. Clin Orthop 244:17-28, 1989.
11. ***Bates D, Ruggieri P.*** Imaging modalities for evaluation of the spine. Radiol Clin North Am 29:675-690, 1991.
12. ***Beekman CE, Hall V.*** Variability of scoliosis measurement from spinal roentgenograms. Phys Ther 59:764-765, 1979.
13. ***Bellah RD, Summerville DA, Treves ST, Micheli LJ.*** Low-back pain in adolescent athletes: detection of stress injury to the pars interarticularis with SPECT. Radiology 180:509-512, 1991.
14. ***Bellus GA, McIntosh I, Smith EA, et al.*** A recurrent mutation in the tyrosine kinase domain of fibroblast growth factor receptor 3 causes hypochondroplasia. Nat Genet 10:357-359, 1995.
15. ***Berns DH, Blaser SI, Modic MT.*** Magnetic resonance imaging of the spine. Clin Orthop 244:78-100, 1989.
16. ***Bethem D, Winter RB, Lowell L, et al.*** Spinal disorders of dwarfism. J Bone Joint Surg (Am) 63:1412-1425, 1981.
17. ***Bethem D, Winter RB, Lutter L.*** Disorders of the spine in diastrophic dwarfism. J Bone Joint Surg (Am) 62:529-536, 1980.
18. ***Bischoff RJ, Rodriguez RP, Gupta K, Righi A, Dalton JE, Whitecloud TS.*** A comparison of computed tomography-myelography, magnetic resonance imaging, and myelography in the diagnosis of herniated nucleus pulposus and spinal stenosis. J Spinal Disord 6:289-295, 1993.
19. ***Boden SD, McCowin PR, Davis DO, Dina TS, Mark AS, Wiesel S.*** Abnormal Magnetic-resonance scans of the cervical spine in asymptomatic subjects. J Bone Joint Surg (Am) 72:1178-1184, 1990.
20. ***Boden SD, Riew DK, Yamaguchi K, Branch TP, Schellinger D, Wiesel SW.*** Orientation of the lumbar facet joints: Association with degenerative disc disease. J Bone Joint Surg (Am) 78:403-411, 1996.
21. ***Borochowitz Z, Berant M, Kristal H.*** Spondylometaphyseal dysplasia: further heterogeneity. Skeletal Radiol 17:181-186, 1988.
22. ***Borochowitz Z, Lachman R, Adomian GE, Spear G, Jones K, Rimoin DL.*** Achondrogenesis type I: delineation of further heterogeneity and identification of two distinct subgroups. J Pediatr 112:23-31, 1988.

23. ***Bowen JR, Ortega K, Ray S, MacEwen GD.*** Spinal deformities in Larsen's syndrome. Clin Orthop 197:159-163, 1985.
24. ***Bradley WG.*** Use of gadolinium chelates in MR imaging of the spine. J Magn Reson Imaging 7:38-46, 1997.
25. ***Braithwaite I, White J, Saifuddin A, Renton P, Taylor BA.*** Vertebral end-plate (Modic) changes on lumbar spine MRI: correlation with pain reproduction at lumbar discography. Eur Spine J 7:363-368, 1998.
26. ***Bram J, Zanetti M, Min K, Hodler J.*** MR abnormalities of the intervertebral disks and adjacent bone marrow as predictors of segmental instability of the lumbar spine. Acta Radiol 39:18-23, 1998.
27. ***Brandt NJ, Friis-Hansen B, Melchior JC.*** Diastrophic dwarfism. Acta Paediatr Scand 60:243 1971.
28. ***Briner J, Brandner M.*** Pathologish-anatomische und radiologische untersuchungen bei zwei fruhgeborenen geschwistern mit diastrophischem zwergwuchs und ausgeprägten wirbelsäulenveränderungen. Virchows Arch A Pathol Anat Histol 364:165-177, 1974.
29. ***Brown BM, Schwartz RH, Frank E, Blank NK.*** Preoperative evaluation of cervical radiculopathy and myelopathy by surface-coil MR imaging. Am J Roentgenol 151:1205-1212, 1988.
30. ***Buckwalter JA.*** Aging and degeneration of the human intervertebral disc. Spine 20:1307-1314, 1995.
31. ***Budorick NE, Pretorius DH, Nelson TR.*** Sonography of the fetal spine: technique, imaging findings, and clinical implications. Am J Roentgenol 164:421-428, 1995.
32. ***Bunnell WP.*** An objective criterion for scoliosis screening. J Bone Joint Surg (Am) 66:1381-1387, 1984.
33. ***Butler D, Trafimow JH, Andersson GBJ, McNeill TW, Huckman MS.*** Discs degenerate before facets. Spine 15:111-113, 1990.
34. ***Byrd SE, Wilczynski MA.*** Imaging modalities for the pediatric spine. Curr Opin Radiol 3:906-918, 1991.
35. ***Campbell MJ, Machin D.*** Medical statistics. pp. 1-189, 2nd ed. John Wiley & Sons, Chichester, 1993.
36. ***Carr AJ, Jefferson RJ, Turner-Smith AR, Beavis A.*** An analysis of normal back shape measured by ISIS scanning. Spine 16:656-659, 1991.
37. ***Cassar-Pullicino VN.*** MRI of the ageing and herniating intervertebral disc. Eur J Radiol 27:214-228, 1998.
38. ***Cobb JR.*** Outline for the study of scoliosis. Inst Course Lect 5:261-275, 1948.
39. ***Collier BD, Johnson RP, Carrera GF, et al.*** Painful spondylolysis or spondylolisthesis studied by radiography and single-photon emission computed tomography. Radiology 154:207-211, 1985.
40. ***Collier BD, Kir KM, Mills BJ, et al.*** Bone scan: a useful test for evaluating patients with low back pain. Skeletal Radiol 19:267-270, 1990.
41. ***Colosimo C, Manfredi R, Tartaglione T.*** Contrast enhancement issues in the MR evaluation of the central nervous system. Eur Radiol 7S:231-237, 1997.
42. ***Coonrad RW, Murrell GAC, Motley G, Lytle E, Hey LA.*** A logical coronal pattern classification of 2,000 consecutive idiopathic scoliosis cases based on the scoliosis research society-defined apical vertebra. Spine 23:1380-1391, 1998.
43. ***Cornelius RS, Leach JL.*** Imaging evaluation of cervical spine trauma. Neuroimag Clin North Am 5:451-463, 1995.
44. ***Coscia ME, Bassett GS, Bowen JR, Ogilvie JW, Winter RB, Simonton SC.*** Spinal abnormalities in camptomelic dysplasia. J Pediatr Orthop 9:6-14, 1989.
45. ***Coste J, Paolaggi JB, Spira A.*** Reliability of interpretation of plain lumbar spine radiographs in benign, mechanical low-back pain. Spine 16:426-428, 1991.
46. ***Daruwalla JS, Balasubramaniam P.*** Moire topography in scoliosis. Its accuracy in detecting the site and size of the curve. J Bone Joint Surg (Br) 67:211-213, 1985.

47. ***Davis PC, Hoffman JC, Jr., Ball TI, et al.*** Spinal abnormalities in pediatric patients: MR imaging findings compared with clinical, myelographic, and surgical findings. Radiology 166:679-685, 1988.
48. ***Delamarter RB, Ross JS, Masaryk TJ, Modic MT, Bohlman, HH.*** Diagnosis of lumbar arachnoiditis by magnetic resonance imaging. Spine 15:304-310, 1990.
49. ***DeSmet AA, Goin JE, Asher MA, Scheuch HG.*** A clinical study of the differences between the scoliotic angles measured on posteroanterior and anteroposterior radiographs. J Bone Joint Surg (Am) 64:489-493, 1982.
50. ***Edeiken-Monroe BS, Edeiken J.*** Imaging of the normal spine, developmental anomalies, and trauma of the spine and extremities. Curr Opin Radiol 4:95-102, 1992.
51. ***el-Khoury GY, Kathol MH, Daniel WW.*** Imaging of acute injuries of the cervical spine: value of plain radiography, CT, and MR imaging. Am J Roentgenol 164:43-50, 1995.
52. ***Espeland A, Korsbrekke K, Albrektsen G, Larsen JL.*** Observer variation in plain radiography of the lumbosacral spine. Br J Radiol 71:266-375, 1998.
53. ***Forese LL, Berdon WE, Harcke HT, et al.*** Severe mid-cervical kyphosis with cord compression in Larsen's syndrome and diastrophic dysplasia: unrelated syndromes with similar radiologic findings and neurosurgical implications. Pediatr Radiol 25:136-139, 1995.
54. ***Foster JW, Dominguez-Steglich MA, Guioli S, et al.*** Campomelic dysplasia and autosomal sex reversal caused by mutations in an SRY-related gene. Nature 372:525-530, 1994.
55. ***Freedman SI, Taber P, Hollister DW, Rimoin DL.*** A lethal form of diastrophic dwarfism. Birth Defects 10:43-49, 1974.
56. ***Frymoyer JW, Newberg A, Pope MH, Wilder DG, Clements J, MacPherson B.*** Spine radiographs in patients with low-back pain. An epidemiological study in men. J Bone Joint Surg (Am) 66:1048-1055, 1984.
57. ***Gates GF.*** SPECT bone scanning of the spine. Semin Nucl Med 28:78-94, 1998.
58. ***Gellis SS, Feingold M.*** Picture of the month. Diastrophic dwarfism. Am J Dis Child 116:525-526, 1968.
59. ***Goldberg MS, Poitras B, Mayo NE, Labelle H, Bourassa R, Cloutier R.*** Observer variation in assessing spinal curvature and skeletal development in adolescent idiopathic scoliosis. Spine 13:1371-1377, 1988.
60. ***Gollop TR, Eigier A.*** Prenatal ultrasound diagnosis of diastrophic dysplasia at 16 weeks. Am J Med Genet 27:321-324, 1987.
61. ***Gore DR, Sepic SB, Gardner GM.*** Roentgenographic findings of the cervical spine in asymptomatic people. Spine 11:521-524, 1986.
62. ***Gundry CR, Fritts HM.*** Magnetic resonance imaging of the musculoskeletal system: The spine, section 3. Clin Orthop 346:262-278, 1998.
63. ***Gundry CR, Heithoff KB.*** Imaging evaluation of patients with spinal deformity. Orthop Clin North Am 25:247-264, 1994.
64. ***Gustavson KH, Holmgren G, Jagell S, Jorulf H.*** Lethal and non-lethal diastrophic dysplasia. A study of 14 Swedish cases. Clin Genet 28:321-334, 1985.
65. ***Hamanishi C, Matukura N, Fujita M, Tomihara M, Tanaka S.*** Cross-sectional area of the stenotic lumbar dural tube measured from the transverse views of magnetic resonance imaging. J Spinal Disord 7:388-393, 1994.
66. ***Hanai K, Kawai K, Itoh Y, Satake T, Fujiyoshi F, Abematsu N.*** Simultaneous measurement of intraosseous and cerebrospinal fluid pressures in lumbar region. Spine 10:64-68, 1985.
67. ***Harvey CJ, Richenberg JL, Saifuddin A, Wolman RL.*** The radiological investigation of lumbar spondylolysis. Clin Radiol 53:723-728, 1998.
68. ***Hastbacka J, de la Chapelle A, Mahtani MM, et al.*** The diastrophic dysplasia gene encodes a novel sulfate transporter: positional cloning by fine-structure linkage disequilibrium mapping. Cell 78:1073-1087, 1994.
69. ***Hastbacka J, Kaitila I, Sistonen P, de la Chapelle A.*** Diastrophic dysplasia gene maps to the distal long arm of chromosome 5. Proc Natl Acad Sci U S A 87:8056-8059, 1990.
70. ***Hastbacka J, Salonen R, Laurila P, de la Chapelle A, Kaitila I.*** Prenatal diagnosis of diastrophic dysplasia with polymorphic DNA markers. J Med Genet 30:265-268, 1993.

71. ***Hastbacka J, Sistonen P, Kaitila I, et al.*** A linkage map spanning the locus for diastrophic dysplasia (DTD). Genomics 11:968-973, 1991.
72. ***Hastbacka J, Superti-Furga A, Wilcox WR, et al.*** Atelosteogenesis type II is caused by mutations in the diastrophic dysplasia sulfate-transporter gene (DTDST): evidence for a phenotypic series involving three chondrodysplasias. Am J Hum Genet 58:255-262, 1996.
73. ***Herring JA.*** The spinal disorders in diastrophic dwarfism. J Bone Joint Surg (Am) 60:177-182, 1978.
74. ***Hertzog RJ.*** Magnetic resonance imaging of the spine. In Frymoyer JW (ed). The adult spine: principles and practice. pp. 457-510, Raven Press Ltd. New York, 1991.
75. ***Hilton RC, Ball J, Benn T.*** Vertebral end-plate lesions (Schmorl's nodes) in the dorsolumbar spine. Ann Rheum Dis 35:127-132, 1976.
76. ***Hollister DW, Lachman RS.*** Diastrophic dwarfism. Clin Orthop 114:61-69, 1976.
77. ***Horton WA.*** Molecular genetics of the human chondrodysplasias-1995. Eur J Hum Genet 3:357-373, 1995.
78. ***Horton WA, Hall JG, Scott CI, Pyeritz RE, Rimoin DL.*** Growth curves for height for diastrophic dysplasia, spondyloepiphyseal dysplasia congenita, and pseudoachondroplasia. Am J Dis Child 136:316-319, 1982.
79. ***Horton WA, Rimoin DL, Lachman RS, et al.*** The phenotypic variability of diastrophic dysplasia. J Pediatr 93:609-613, 1978.
80. ***Horton WA.*** Extending the nosology of the chondrodysplasias to the cellular and molecular levels. Pediatr Radiol 24:410-412, 1994.
81. ***Horton WA, Hecht JT.*** The Chondrodysplasias. In Royce PM, Steinmann B (eds). Connective Tissue and Its Heritable Disorders. pp. 641-675, Wiley-Liss, New York, 1993.
82. ***Horton WA, Rimon DL, Hollister DL, Silberberg R.*** Diastrophic dwarfism: a histochemical an ultrastructural of the endochondral growth plate. Pediatr Res 13:904-909, 1979.
83. ***Hultman G, Saraste H, Ohlsen H.*** Anthropometry, spinal canal width, and flexibility of the spine and hamstring muscles in 45-55-year-old men with and without low back pain. J Spinal Disord 5:245-253, 1992.
84. ***Inufusa A, An HS, Lim TH, Hasegawa T, Haughton VM, Nowicki BH.*** Anatomic changes of the spinal canal and intervertebral foramen associated with flexion-extension movement. Spine 21:2412-2420, 1996.
85. ***Jahre C, Sze G.*** Magnetic resonance imaging of spinal metastases. Top Magn Reson Imaging 1:63-70, 1988.
86. ***James JIP.*** Infantile idiopathic scoliosis. Clin Orthop 77:57-72, 1970.
87. ***James JIP, Lloyd-Roberts GC, Pilcher M.*** Infantile structural scoliosis. J Bone Joint Surg (Br) 41:719-735, 1959.
88. ***Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS.*** Magnetic resonance imaging of the lumbar spine in people without back pain. New Engl J Med 331:69-73, 1994.
89. ***Jinkins JR, Runge VM.*** The use of MR contrast agents in the evaluation of disease of the spine. Top Magn Reson Imaging 7:168-180, 1995.
90. ***Johnston CE, Birch JG, Daniels JL.*** Cervical kyphosis in patients who have Larsen syndrome. J Bone Joint Surg (Am) 78:538-545, 1996.
91. ***Jung C, Sohn C, Sergi C.*** Case report: prenatal diagnosis of diastrophic dysplasia by ultrasound at 21 weeks of gestation in a mother with massive obesity. Prenat Diagn 18:378-383, 1998.
92. ***Kaiser JA, Holland BA.*** Imaging of the cervical spine. Spine 23:2701-2712, 1998.
93. ***Kaitila I.*** Diastrophic dysplasia. In Eriksson A, Forsius H, Nevanlinna H, Workman P, Norio R (eds). Population Structure and Genetic Disorders. pp. 610-613, Academic Press, London, 1980.
94. ***Kaitila I, Ammala P, Karjalainen O, Liukkonen S, Rapola J.*** Early prenatal detection of diastrophic dysplasia. Prenat Diagn 3:237-244, 1983.
95. ***Kaitila I, Ammala P, Karjalainen O, Liukkonen S, Rapola J.*** Vaikean kääpiökasvuisuuden, diastrofisen dysplasian toteaminen varhaisraskauden aikana. Duodecim 99:861-868, 1983.

96. ***Kaitila I, Marttinen E, Merikanto J, Poussa M, Ryöppy S.*** Clinical expression and course of diastrophic dysplasia. Am J Med Genet 24:141 1989.
97. ***Karantanas AH, Zibis AH, Papaliaga M, Georgiou E, Rousogiannis S.*** Dimensions of the lumbar spinal canal: variations and correlations with somatometric parameters using CT. Eur Radiol 8:1581-1585, 1998.
98. ***Karlstedt E, Isotalo E, Haapanen ML, Kalland M, Pirinen S, Kaitila I.*** Correlation between speech outcome and cephalometric dimensions in patients with diastrophic dysplasia. J Cran Genet Dev Bio 18:38-43, 1998.
99. ***Karlstedt E, Kaitila I, Pirinen S.*** Craniofacial structure in diastrophic dysplasia - a cephalometric study. Am J Med Genet 72:266-274, 1997.
100. ***Kash IJ, Sane SM, Samaha FJ, Briner J.*** Cervical cord compression in diastrophic dwarfism. J Pediatr 84:862-864, 1974.
101. ***Kelen GD, Noji EK, Doris PE.*** Guidelines for use of lumbar spine radiography. Ann Emerg Med 15:245-251, 1986.
102. ***King HA, Moe JH, Bradford DS, Winter RB.*** The selection of fusion levels in thoracic idiopathic scoliosis. J Bone Joint Surg (Am) 65:1301-1313, 1983.
103. ***Kniest W.*** Zur Abgrenzung der Dysostosis enchondralis von der Chondrodystrophie. Z Kinderheilk 43:633-640, 1952.
104. ***Kopits SE.*** Orthopedic complications of dwarfism. Clin Orthop 114:153-179, 1976.
105. ***Kozlowski K, Barylak A.*** Diastrophic dwarfism. Australas Radiol 18:398-406, 1974.
106. ***Krecak J, Starshak RJ.*** Cervical kyphosis in diastrophic dwarfism: CT and MR findings. Pediatr Radiol 17:321-322, 1987.
107. ***Kretzschmar K.*** Degenerative diseases of the spine. The role of myelography and myelo-CT. Eur J Radiol 27:229-234, 1998.
108. ***Kubik-Huch RA, Wisser J, Stallmach T, Ladd ME, Meier A, Marincek B.*** Prenatal diagnosis of fetal malformations by ultrafast magnetic resonance imaging. Prenat Diagn 18:1205-1208, 1998.
109. ***Kulkarni MV, McArdle CB, Kopanicky D, et al.*** Acute spinal cord injury: MR imaging at 1.5 T. Radiology 164:837-843, 1987.
110. ***Lachman R, Hall JG.*** The radiographic prenatal diagnosis of the generalized bone dysplasias and other skeletal abnormalities. Birth Defects 15:3-24, 1979.
111. ***Lachman R, Sillence D, Rimoin D, et al.*** Diastrophic dysplasia: the death of a variant. Radiology 140:79-86, 1981.
112. ***Lachman RS.*** Fetal imaging in the skeletal dysplasias: overview and experience. Pediatr Radiol 24:413-417, 1994.
113. ***Lachman RS.*** The cervical spine in the skeletal dysplasias and associated disorders. Pediatr Radiol 27:402-408, 1997.
114. ***Lamy M, Maroteaux P.*** Le nanisme diastrophique. Presse Med 68:1977-1980, 1960.
115. ***Langenskiöld A, Ritsila V.*** Congenital dislocation of the patella and its operative treatment. J Pediatr Orthop 12:315-323, 1992.
116. ***Langer LO.*** Diastrophic dwarfism in early infancy. Am J Roentgenol 93:399-404, 1965.
117. ***Larsen LJ, Schottstaedt ER, Bost FC.*** Multiple congenital dislocations associated with characteristic facial abnormality. J Pediat 37:574-581, 1950.
118. ***Lewonowski K, King JD, Nelson MD.*** Routine use of magnetic resonance imaging in idiopathic scoliosis patients less than eleven years of age. Spine 17:S109-16, 1992.
119. ***Liang MH, Katz JN, Frymoyer JW.*** Plain Radiographs in Evaluating the Spine. In Frymoyer JW (ed). The adult spine: Principles and practice. pp. 289-307, Raven Press Ltd. New York, 1991.
120. ***Lusins JO, Elting JJ, Cicoria AD, Goldsmith SJ.*** SPECT evaluation of lumbar spondylolysis and spondylolisthesis. Spine 19:608-612, 1994.
121. ***Macpherson RI, Genez B.*** Spine. In Reed MH (ed). Pediatric Skeletal Radiology. pp. 209-296, Williams & Wilkins, Baltimore, 1992.
122. ***Manelfe C.*** Imaging of the spine and spinal cord. Curr Opin Radiol 3:5-15, 1991.

123. Mantagos S, Weiss RR, Mahoney M, Hobbins JC. Prenatal diagnosis of diastrophic dwarfism. Am J Obstet Gynecol 139:111-113, 1981.

124. Maroteaux P, Lamy M, Bernard J. La dysplasie spondylo-epiphysaire tradive. Presse Med 65:1205-1208, 1957.

125. Maroteaux P, Lamy M, Robert JM. Le nanisme thanatophore. Presse Med 75:2519-2524, 1967.

126. Matsumoto M, Fujimura Y, Suzuki N, et al. MRI of cervical intervertebral discs in asymptomatic subjects. J Bone Joint Surg (Br) 80-B:19-24, 1998.

127. Matsuyama Y, Winter RB, Loenstein JE. The spine in diastrophic dysplasia - The surgical arthrodesis of thoracic and lumbar deformities in 21 patients. Spine 24:2325-2331, 1999.

128. Mäkitie O, Kaitila I. Growth in diastrophic dysplasia. J Pediatr 130:641-646, 1997.

129. McKusick VA. Metaphyseal dysostosis and thin hair: a “new” recessively inherited syndrome? Lancet 1:832-833, 1964.

130. McMaster MJ. Infantile idiopathic scoliosis. In Bradford DS, Hensinger RM (eds). The Pediatric Spine. pp. 218-232, Thieme Inc, New York, 1985.

131. Modic MT, Masaryk TJ, Ross JS, Carter JR. Imaging of degenerative disk disease. Radiology 168:177-186, 1988.

132. Modic MT, Ross JS, Masaryk TJ. Imaging of degenerative disease of the cervical spine. Clin Orthop 239:109-120, 1989.

133. Modic M, Steinberg P, Ross J, Masaryk T, Carter J. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. Radiology 166:193-199, 1988.

134. Morrissy RT, Goldsmith GS, Hall EC, Kehl D, Cowie GH. Measurement of the Cobb angle on radiographs of patients who have scoliosis. Evaluation of intrinsic error. J Bone Joint Surg (Am) 72:320-327, 1990.

135. Nokes SR, Murtagh FR, Jones JD, 3d, et al. Childhood scoliosis: MR imaging. Radiology 164:791-797, 1987.

136. Nordwall A. Studies in idiopathic scoliosis relevant to etiology, conservative and operative treatment. Acta Orthop Scand 1S:1-178, 1973.

137. O’Brien GD, Rodeck C, Queenan JT. Early prenatal diagnosis of diastrophic dwarfism by ultrasound. Br Med J 280:1300 1980.

138. Ogden JA, Ganey TM, Sasse J, Neame PJ, Hilbelink DR. Development and Maturation of the Axial skeleton. In Weinstein SL (ed). The Pediatric Spine: Principles and Practice. pp. 3-69, Raven Press, Ltd. New York, 1994.

139. Okada Y, Ikata T, Katoh S, Yamada H. Morphologic analysis of the cervical spinal cord, dural tube, and spinal canal by magnetic resonance imaging in normal adults and patients with cervical spondylotic myelopathy. Spine 19:2331-2335, 1994.

140. Ounsted MK, Moar VA, Scott WA. Growth and proportionality in early childhood. Early Hum Dev 14:49-60, 1986.

141. Parkkola R, Kormano M. Lumbar disc and back muscles degeneration on MRI; correlation to age and body mass. J Spinal Disorders 5:86-92, 1992.

142. Parkkola R, Rytökoski U, Kormano M. Magnetic resonance imaging of the discs and trunk muscles in patients with low back pain and healthy control subjects. Spine 18:830-836, 1993.

143. Parrot JM. Sur les malformations achondroplasiques et le Dieu Ptah. Bull Soc Antropol 1:296 1878. Cited in Scott, CI. Achondroplastic and hypochondroplastic dwarfism. Clin Orthop 114:18-29, 1976.

144. Paterson CR, McAllion S, Miller R. Heterogeneity of osteogenesis imperfecta type I. J Med Genet 20:203-205, 1983.

145. Pathria MN, Petersilge CA. Spinal trauma. Radiol Clin North Am 29:847-865, 1991.

146. Pearson JD, Dangerfield PH, Atkinson JT, et al. Measurement of body surface topography using an automated imaging system. Acta Orthop Belg 58S:73-79, 1992.

147. Peltonen J, Merikanto J. Ilizarovin menetelmä rigidin nilkka-jalkaterä-deformiteetin korjaamisessa diastrofista dysplasiaa sairastavilla potilailla. SOT 16:222-225, 1993.

148. Peltonen J, Vaara P, Marttinen E, Ryoppy S, Poussa M. The knee joint in diastrophic dysplasia. A clinical and radiological study. J Bone Joint Surg (Br) 81:625-631, 1999.

149. Peltonen JI, Hoikka V, Poussa M, Paavilainen T, Kaitila I. Cementless hip arthroplasty in diastrophic dysplasia. J Arthroplasty 7S:369-376, 1992.

150. Perheentupa J. Kolme periytyvää kasvuhäiriötä. Duodecim 88:60-71, 1972.

151. Post MJ, Bowen BC, Sze G. Magnetic resonance imaging of spinal infection. Rheum Dis Clin North Am 17:773-794, 1991.

152. Poussa M, Merikanto J, Ryoppy S, Marttinen E, Kaitila I. The spine in diastrophic dysplasia. Spine 16:881-887, 1991.

153. Queenan JT, O'Brien GD, Campbell S. Ultrasound measurement of fetal limb bones. Am J Obstet Gynecol 138:297-302, 1980.

154. Qureshi F, Jacques SM, Johnson SF, et al. Histopathology of fetal diastrophic dysplasia. Am J Med Genet 56:300-303, 1995.

155. Raininko R, Manninen H, Battié MC, Gibbons LE, Gill K, Fisher LD. Observer variability in the assessment of disc degeneration on magnetic resonance images of the lumbar and thoracic spine. Spine 20:1029-1035, 1995.

156. Richards BS. Atlanto-axial instability in diastrophic dysplasia. A case report. J Bone Joint Surg (Am) 73:614-616, 1991.

157. Rimoin DL. Clinical variability in achondroplasia. Basic Life Sci 48:123-127, 1988.

158. Rimoin RD, Lachman RS. Genetic disorders of the osseous skeleton. In Beighton P (ed). McKusick's heritable disorders of connective tissue. pp. 557-689, Mosby, St. Louis, 1993.

159. Rimoin RD, Lachman RS. Chondrodysplasias. In Rimoin DL, Connor MJ, Pyeritz RE (eds). Emery and Rimoin's Principles and Practice of Medical Genetics. pp. 2779-2815, Churchill Livingstone, New York, 1997.

160. Rintala A, Marttinen E, Rantala SL, Kaitila I. Cleft palate in diastrophic dysplasia. Morphology, results of treatment and complications. Scand J Plast Reconstr Surg 20:45-49, 1986.

161. Rizzolo SJ, Vaccaro AR, Cotler JM. Cervical spine trauma. Spine 19:2288-2298, 1994.

162. Rogers JG, Perry MA, Rosenberg LA. IQ measurement in children with skeletal dysplasias. Pediatrics 63:894-897, 1979.

163. Ross JS, Modic MT. Current assessment of spinal degenerative disease with magnetic resonance imaging. Clin Orthop 279:68-81, 1992.

164. Ross JS, Perez-Reyes N, Masaryk TJ, Bohlman H, Modic MT. Thoracic disk herniation. MR imaging. Radiology 165:511-515, 1987.

165. Rossi A, van der Harten H., Beemer F, et al. Phenotypic and genotypic overlap between atelosteogenesis type 2 and diastrophic dysplasia. Hum Genet 98:657-661, 1996.

166. Ryoppy S, Poussa M, Merikanto J, Marttinen E, Kaitila I. Deformities if the lower extremities in diastrophic dysplasia. Acta Orthop Scand 61(suppl 237):49-50, 1990.

167. Ryoppy S, Poussa M, Merikanto J, Marttinen E, Kaitila I. Foot deformities in diastrophic dysplasia. An analysis of 102 patients. J Bone Joint Surg (Br) 74:441-444, 1992.

168. Saifuddin A, Burnett SJ, White J. The variation of position of the conus medullaris in an adult population. A magnetic resonance imaging study. Spine 23:1452-1456, 1998.

169. Saifuddin A, Noordeen H, Taylor BA, Bayley I. The role of imaging in the diagnosis and management of thoracolumbar burst fractures: current concepts and a review of the literature. Skeletal Radiol 25:603-613, 1996.

170. Saifuddin A, White J, Tucker S, Taylor BA. Orientation of lumbar pars defects: implications for radiological detection and surgical management. J Bone Joint Surg (Br) 80:208-211, 1998.

171. Sato N, Sze G. Extradural spinal meningioma: MRI. Neuroradiology 39:450-452, 1997.

172. Scheck M, Parker J, Daentl D. Hyaline cartilage changes in diastrophic dwarfism. Virchows Arch A Pathol Anat Histol 378:347-359, 1978.

173. Schenk AK. Achondroplasia in humans Orthopedic Hospital, Military Medical Academy, St. Petersburg, Russia; 1910. Cited in reference #114.

174. Sevastikoglou JA, Bergquist E. Evaluation of the reliability of radiological methods for registration of scoliosis. Acta Orthop Scand 40:608-613, 1969.

175. Shapiro F. Light and electron microscopic abnormalities in diastrophic dysplasia growth cartilage. Calcif Tissue Int 51:324-331, 1992.

176. Shiang R, Thompson LM, Zhu YZ, et al. Mutations in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism, achondroplasia. Cell 78:335-342, 1994.

177. Sillence D, Kozlowski K, Bar-ziv J, Fuhrumann-Rieger A, Fuhrmann W, Pascu F. Perinatally lethal short rib-polydactyly syndromes. 1. Variability in known syndromes. Pediatr Radiol 17:474-480, 1987.

178. Sillence DO, Kozlowski K, Rogers JG, Sprague PL, Cullity GJ, Osborn RA. Atelosteogenesis: evidence for heterogeneity. Pediatr Radiol 17:112-118, 1987.

179. Sillence DO, Horton WA, Rimoin RD. Morphologic studies in the skeletal dysplasias. J Am Pathol 96:811-870, 1979.

180. Smith AS, Blaser SI. Infectious and inflammatory processes of the spine. Radiol Clin North Am 29:809-827, 1991.

181. Smoker WR. Craniovertebral junction: Normal anatomy, craniometry and congenital anomalies. Radiographics 14:255-277, 1994.

182. Spranger J. International classification of osteochondrodysplasias. The International Working Group on Constitutional Diseases of Bone. Eur J Pediatr 151:407-415, 1992.

183. Spranger JW, Wiedemann H-R. Dysplasia spondyloepiphysaria congenita. Helv Paediat Acta 21:598-611, 1966.

184. Stanescu V, Stanescu R, Maroteaux P. Letter to the editor: growth cartilage of diastrophic dwarfism. Pediatr Res 14:965 1980.

185. Stanescu V, Stanescu R, Maroteaux P. Pathogenic mechanisms in osteochondrodysplasias. J Bone Joint Surg (Am) 66:817-836, 1984.

186. Stokes IA, Moreland MS. Concordance of back surface asymmetry and spine shape in idiopathic scoliosis. Spine 14:73-78, 1989.

187. Stover CN, Hayes JT, Holt JF. Diastrophic Dwarfism. Am J Roentgenol 89:914-922, 1963.

188. Stuve A, Wiedemann H-R. Congenital bowing of the long bones in two sisters. Lancet I:495 1971.

189. Superti-Furga A, Hastbacka J, Rossi A, et al. A family of chondrodysplasias caused by mutations in the diastrophic dysplasia sulfate transporter gene and associated with impaired sulfation of proteoglycans. Ann N Y Acad Sci 785:195-201, 1996.

190. Superti-Furga A, Hastbacka J, Wilcox WR, et al. Achondrogenesis type IB is caused by mutations in the diastrophic dysplasia sulphate transporter gene. Nat Genet 12:100-102, 1996.

191. Superti-Furga A, Neumann L, Riebel T, et al. Recessively inherited multiple epiphyseal dysplasia with normal stature, club foot, and double layered patella caused by a DTDST mutation. J Med Genet 36:621-624, 1999.

192. Superti-Furga A, Rossi A, Steinmann B, Gitzelmann R. A chondrodysplasia family produced by mutations in the diastrophic dysplasia sulfate transporter gene: genotype/phenotype correlations. Am J Med Genet 63:144-147, 1996.

193. Sze G. MR imaging of the spinal cord: current status and future advances. Am J Roentgenol 159:149-159, 1992.

194. Sze G, Krol G, Zimmerman RD, Deck MD. Intramedullary disease of the spine: diagnosis using gadolinium-DTPA-enhanced MR imaging. Am J Roentgenol 151:1193-1204, 1988.

195. Tanner JM, Hayashi T, Preece MA, Cameron N. Increase in length of leg relative to trunk in Japanese children and adults from 1957 to 1977: comparison with British and with Japanese Americans. Ann Hum Biol 9:411-423, 1982.

196. Tarr RW, Drolshagen LF, Kerner TC, Allen JH, Partain CL, James AE, Jr. MR imaging of recent spinal trauma. J Compu Assist Tomo 11:412-417, 1987.

197. Tavormina PL, Shiang R, Thompson LM, et al. Thanatophoric dysplasia (types I and II) caused by distinct mutations in fibroblast growth factor receptor 3. Nat Genet 9:321-328, 1995.

198. Taybi H. Diastrophic dwarfism. Radiology 80:1-10, 1963.

199. Taylor JR. Growth of human intevertebral discs and vertebral bodies. J Anat 120:49-68, 1975.

200. Tehranzadeh J, Wang F, Mesgarzadeh M. Magnetic resonance imaging of osteomyelitis. Crit Rev Diagn Imag 33:495-534, 1992.
201. Teplick JG, Laffey PA, Berman A, Haskin ME. Diagnosis and evaluation of spondylolisthesis and/or spondylolysis on axial CT. Am J Neuroradiol 7:479-491, 1986.
202. Tertti M, Paajanen H, Laato M, Aho H, Komu M, Kormano M. Disc degeneration in magnetic resonance imaging. A comparative biochemical, histologic, and radiologic study in cadaver spines. Spine 16:629-634, 1991.
203. Thornbury JR, Fryback DG, Turski PA, et al. Disk-caused nerve compression in patients with acute low-back pain: diagnosis with MR, CT myelography, and plain CT. Radiology 186:731-738, 1993.
204. Tolo VT. Spinal deformity in short-stature syndromes. Instr Course Lect 39:399-405, 1990.
205. Tolo VT, Kopits SE. Spinal deformity in diastrophic dysplasia. Orthop Trans 7:31-32, 1983.
206. Tolo VT. Spinal Deformity in Dwarfs. In Bradford DS, Hensinger RM (eds). The Pediatric Spine. pp. 338-349, Thieme Inc. New York, 1985.
207. Tolo VT. Spinal Deformity in Skeletal Dysplasias. In Weinstein SL (ed). The Pediatric Spine: Principles and Practice. pp. 369-393, Raven Press Ltd. New York, 1994.
208. Toyone T, Takahashi K, Kitahara H, Yamagata M, Murakami M, Moriya H. Vertebral bone marrow changes in degenerative lumbar disc disease. J Bone Joint Surg (Br) 76:757-764, 1994.
209. Tracy PT, Wright RM, Hanigan WC. Magnetic resonance imaging of spinal injury. Spine 14:292-301, 1989.
210. Ulm MR, Kratochwil A, Oberhuemer U, Ulm B, Blaicher W, Bernaschek G. Ultrasound evaluation of fetal spine length between 14 and 24 weeks of gestation. Prenat Diagn 19:637-641, 1999.
211. Vaara P, Marttinen E, Peltonen J. Ultrasonography of the patellofemoral joint in diastrophic dysplasia. J Pediatr Orthop 17:512-515, 1997.
212. Vaara P, Peltonen J, Poussa M, et al. Development of the hip in diastrophic dysplasia. J Bone Joint Surg (Br) 80:315-320, 1998.
213. Vaara P, Sintonen H, Peltonen J, Hokkanen H, Poussa M, Ryöppy S. Health-related quality of life in patients with diastrophic dysplasia. Scand J Public Health 1:38-42, 1999.
214. Vazquez AM, Lee FA. Diastrophic dwarfism. J Pediatr 72:234-242, 1968.
215. Walker BA, Scott CI, Hall JG, Murdoch JL, McKusick VA. Diastrophic dwarfism. Medicine (Baltimore) 51:41-59, 1972.
216. Weinstein SL. Adolescent idiopathic scoliosis - prevalence and natural history. In Weinstein SL (ed). The Pediatric Spine: Principles and Practice. pp. 463-478, Raven Press, Ltd. New York, 1994.
217. Willner S. Moire topography - a method for school screening of scoliosis. Arch Orthop Traum Surg 95:181-185, 1979.
218. Wilson DA, Prince JR. John Caffey award. MR imaging determination of the location of the normal conus medullaris throughout childhood. Am J Roentgenol 152:1029-1032, 1989.
219. Wilson DW, Chrispin AR, Carter CO. Diastrophic dwarfism. Arch Dis Child 44:48-58, 1969.
220. Wong HK, Balasubramaniam P, Rajan U, Chng SY. Direct spinal curvature digitization in scoliosis screening—a comparative study with Moire contourgraphy. J Spin Disord 10:185-192, 1997.
221. Wood KB, Garvey TA, Gundry C, Heithhoff KB. Magnetic resonance imaging of the thoracic spine. J Bone Joint Surg (Am) 77:1631-1638, 1995.
222. Wynne-Davies R, Hall C. Two clinical variants of spondylo-epiphysial dysplasia congenita. J Bone Joint Surg (Br) 64:435-441, 1982.
223. Ylikoski M, Tallroth K. Measurement variations in scoliotic angle, vertebral rotation, vertebral body height, and intervertebral disc height space. J Spinal Disord 3:387-391, 1990.
224. Zamani AA, Moriarty T, Hsu L, et al. Functional MRI of the lumbar spine in erect position in a superconducting open-configuration MR system: preliminary results. J Magn Reson Imaging 8:1329-1333, 1998.