Eur J Pediatr (1997) 156: 214–223

MEDICAL GENETICS

A. Giedion · E. Boltshauser · J. Briner · G. Eich
G. Exner · H. Fendel · L. Kaufmann · B. Steinmann
J. Spranger · A. Superti-Furga

Heterogeneity in Schwartz-Jampel chondrodystrophic myotonia

Received: 26 July 1996 / Accepted: 24 September 1996

Abstract The Schwartz-Jampel syndrome (SJS; chondrodystrophic myotonia; McK 255800) is a recessively inherited condition defined by myotonia, short stature, and bone dysplasia. Genetic linkage between SJS and chromosomal region 1q36-34 has been observed in several families, but the gene has not yet been identified. We studied the clinical and radiological features in 81 patients from the literature and 5 own patients trying to identify distinct subgroups. In addition, we tested genetic linkage to the SJS locus on chromosome 1 in one family with two affected sibs. We found that a group of patients have mild skeletal changes which may be secondary consequences of myotonia, while another group of patients appear to have primary bone dysplasia with myotonia. Within this latter group, there are differences in age of manifestation, clinical course and pattern of bone changes. We tentatively isolate three different types of SJS: type 1A, usually recognized in childhood, with moderate bone dysplasia, corresponding to the original descriptions of Schwartz, Jampel and Aberfeld; type 1B, similar to type 1A but recognizable at birth, with more pronounced bone dysplasia resembling Kniest dysplasia; and type 2, manifest at birth, with increased mortality and bone dysplasia resembling Pyle disease. Genetic analysis of the family with two sibs affected by SJS type 2 showed evidence against linkage to chromosome 1p36-34.

Conclusions SJS is clinically and radiologically heterogeneous. The causes of heterogeneity are not known yet but are likely to include both different mutations at the SJS locus on chromosome 1 and the presence of a second SJS locus. A tentative clinico-radiological classification can be useful for the characterization of patients and the development of genotype-phenotype correlations.

Key words Schwartz-Jampel syndrome
Osteochondrodysplasia · Myotonia · Short stature
Genetic linkage

Abbreviation *SJS* Schwartz-Jampel Syndrome

Introduction

Reviewing the clinical and radiological findings in five own patients who had been given the diagnosis of Schwartz-Jampel syndrome (SJS), we were impressed by the wide variation between individuals. The study of 57 papers reporting 81 patients under the diagnosis of SJS or one of its other denominations (chondrodystrophic myotonia; myotonic myopathy, dwarfism, chondrodystrophy and ocular and facial abnormalities; Schwartz-Jampel-Aberfeld syndrome; Catel-Hempel syndrome) confirmed our impression that the diagnosis of SJS has been given to patients with different clinical and radiological phenotypes. We analysed the natural history of clinical and radiological changes in our own patients and those in the literature looking for similarities between cases which might point to the existence of distinct subgroups. As a result, we propose a tentative classification of SJS which may serve as a "working classification" awaiting molecular classification. References are made only to publications directly relevant to our discussion.

J. Briner
Institute of Clinical Pathology, University Hospital, CH-8091 Zurich, Switzerland

G. Exner
Orthopaedic Clinic Balgrist, University of Zürich, Switzerland

H. Fendel
Von Haunersches Kinderspital, University of München, Germany

J. Spranger
Kinderklinik, Johnannes Gutenberg University, Mainz, Germany

A. Giedion (✉) · E. Boltshauser · G. Eich · L. Kaufmann
B. Steinmann · A. Superti-Furga (✉)
University Children's Hospital, Steinwiesstrasse 75,
CH-8032 Zurich, Switzerland
Fax: +41-1-266-7171
Email: asuperti @hispi.unizh.ch

Case reports

Clinical findings

The main clinical findings in our five cases are shown in Table 1. Some features will be commented on briefly. Birth length was normal in cases 3 and 4 but diminished in cases 2 and 5 (sib of case 4). Case 4 deceased at age 3 months during acute gastro-enteritis. Height in childhood was moderately or markedly decreased in all surviving patients. In case 2, bone dysplasia was manifest at birth but myotonia was not, and the original diagnosis was "Kniest-like bone dysplasia"; SJS was diagnosed only at the age of 5.5 years. In case 4 SJS was diagnosed shortly after birth, in his sister (case 5) at 17 weeks of gestation by ultrasound [13]. In these three cases, short extremities in the newborn were explicitly recorded. A characteristic appearance of the face (Fig. 1) was observed in all cases. Percussion myotonia was absent in cases 2 and 5, not examined in case 4 and not mentioned in cases 1 and 3. Muscular hypertrophy was seen in case 1 only (Fig. 1B), who also had long-lasting stiffness after passive movements of the extremities. Muscle stiffness, joint contractures, outward rotation (probably caused by increased traction of the gluteal muscles) and bowing of the lower extremities led to late ambulation, orthopaedic problems of varying severity, and to the characteristic chaplinesque gait in all surviving cases (Fig. 1B). Concentric needle electromyography (EMG) was performed in all five cases. It displayed spontaneous, continuous high frequency low voltage discharges as well as frequent high frequency, low voltage wax-and-wane "dive bomber" discharges, at rest and on needle movement and insertion in all cases, as well as following percussion (in selected muscles) in case 2, 3 and 5. In case 2, curare was given during general anaesthesia for intubation and myotonic discharges were suppressed. In case 5, intensity of myotonia diminished markedly from age 2 weeks to age 10 months and slightly further until age 8 years. Muscle biopsy was performed in cases 3 (unspecific myopathic pattern, type I fibres dominating over type II) and 4 (normal results). Blood cell counts or blood chemistry did not show specific changes in any case. Immunological workup in case 3, made because of repeated infections, was normal.

Skeletal radiologic findings

Case 1 (Fig. 2)

Radiographs were available at the age of 2–2.5 years. Main findings were: generalized moderate osteoporosis, moderately flattened lower thoracic and upper lumbar vertebral bodies with mild anterior scalloping, slightly flared iliac wings, steep acetabular roofs, moderately shortened long bones with round and bulbous epiphyses of proximal humerus, distal femur and proximal tibia, slightly flattened femoral heads with irregular structure suggesting incipient fragmentation.

Case 2 (M.H.) (Fig. 3)

In the newborn period, the findings of a short-limbed dwarfism, with plump, dumbbell shaped and bowed femora and tibiae were reminiscent of Kniest dysplasia [15]. Other findings were flattened and elongated lumbar vertebral bodies with coronal clefting of L1, flared iliac wings with a notch at the lateral acetabular angle, prominent glenoid process of the scapulae with obtuse inferior angle. Within the 1st year of life, generalized osteoporosis developed. Follow up over 14 years showed regression of the spinal changes. Minimal scoliosis was noted. The coccyx was not ossified. The epiphyses of the long bones, in particular of the retrocurvated knees, proximal humerus, and elbow, were moderately enlarged (but the femoral heads were not) and the metaphyses were slightly widened. An MRI study of the left knee at 13.5 years showed marked epimetaphyseal changes. The femoral heads were small and irregular, the femoral necks were enlarged.

Case 3 (Fig. 4)

In infancy, the findings were reminiscent of those in case 2 including a prominent glenoid process of the scapula, platyspondyly (but no coronal clefts), and Kniest dysplasia-like configuration of pelvis and lower extremities. The ischiopubic synchondrosis was unusually wide both in infancy and in childhood.

Table 1 Synopsis on clinical features of five cases with SJS

Case	1	2	3	4	5
Family history	Unremarkable	Unremarkable	Unremarkable	Siblings	
Sex	Male	Male	Female	Male	Female
Weight at birth	3.6 kg (+ 0.4 SD)	2.4 kg (− 2 SD)	3.9 kg (+ 1.4 SD)	3.9 kg (+ 1 SD)	2.85 kg (− 1 SD)
Length at birth	Unknown	43 cm (− 3.4 SD)	50.5 cm (+ 0.3 SD)	52 cm (+ 0.6 SD)	46 cm (− 2.1 SD)
Length, evolution	2.5 years, 83 cm (− 2.6 SD)	123 cm at 14 years (− 4.8 SD)	89 cm at 4.3 years (− 4.8 SD)	59 cm at 11 wks (0 SD)	112 cm at 8.2 yrs (− 3.6 SD)
Short extremities: age when first noticed	Unknown	Birth	Unknown	Birth	Prenatal
Intelligence	Normal	Low-normal	Normal	(Normal)	Normal
"Whistling" face	2.5 years	1.6 years	Unknown	Birth	Birth
Age when SJS was diagnosed	2.5 years	5.5 years	4.3 years	5 days	Prenatal
EMG changes, age when first recognized	2.5 years	5.5 years	4.3 years	3 weeks	3 weeks
Other significant findings	Myopia	Neurogenic myotonia; cataract left eye, myopia right eye (18 diopters); narrow larynx; hiatal hernia; hydronephrosis and hydroureter, renal stones; testicular torsion; coccyx not ossified	Myopia, 8 diopters; bilateral posterior cataracts; Wolff-Parkinson-White Syndrome; both femoral heads visible and palpable because of anteversion	Abnormal EEG; gastro-esophageal reflux; recurrent infections; death during enteritis at age 3 months; coccyx not ossified	Surgical rectification of tibiae at age 1.5 years "Disappearance" of femoral heads at age 6.7 years

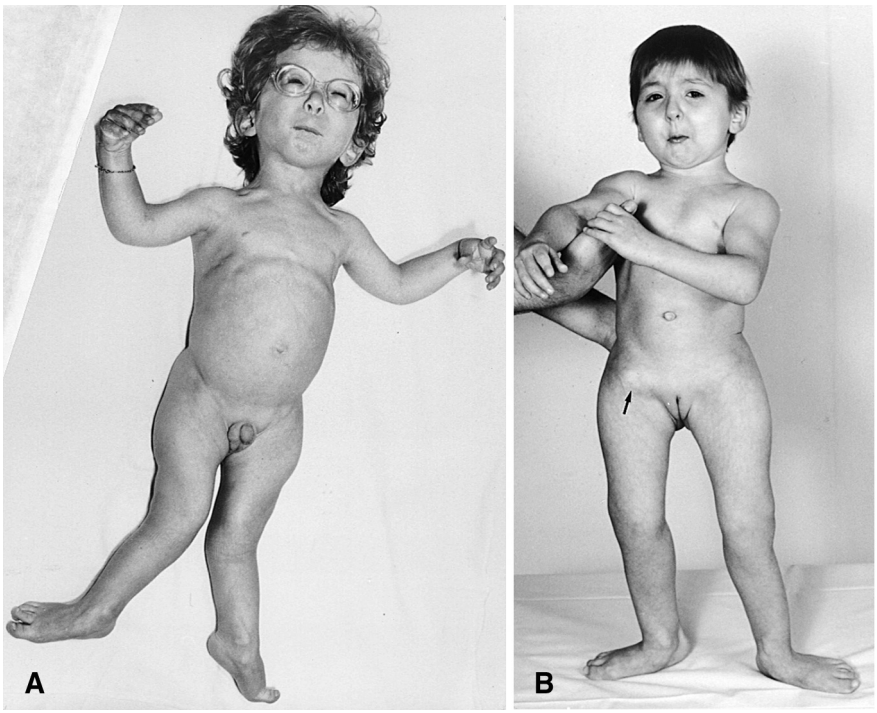


Fig. 1 Characteristic appearance of cases with SJS (**A**) case 2 (2.5 years). Mask-like facial expression, blepharospasm, myopia, stiff mouth, external rotation of legs with recurvation of knees, poor muscle bulk (**B**) case 3 (4.3 years). Similar to **A**, but lips pursed, muscular hypertrophy, prominence of femoral heads in groins (*arrow*)

Case 4 (S.W.) (Fig. 5)

Observation time is limited to 3 months. Birth length was normal, but the clinical and radiological pattern at birth suggested short-limbed bone dysplasia with marked anterior and lateral bowing, mild metaphyseal flaring and external rotation of the lower extremities. The base of the skull was moderately sclerosed (sclerosis of the upper margins of the orbits produced a "mephistophelian" appearance), the occiput was flattened, and there were more than 25 small and two large Wormian bones in the sagittal and lambdoid sutures. At 3 months, generalized osteoporosis was evident, the metaphyseal margins at the growth plate had blurred and the adjacent metaphysis was irregular, particularly in the proximal humerus and femoral neck. The vertebral bodies were slightly globular with calcified chordal rests visible in the lumbar region. The dens was normally developed, the coccyx was unossified, and there was flaring of the iliac wings, without notches.

Case 5 (F.W.) (sister of case 4; Fig. 6)

Short and bowed femora (with fetal hypokinesia) were seen on ultrasound examination at pregnancy week 17 [13]. Neonatal findings were similar to those in the elder brother (case 4; see above). Beginning in the 2nd year of life, severe metaphyseal undertubulation of the long bones reminiscent of Pyle disease was noted, most marked at the knee and proximal humerus. At these sites, osteoporosis with coarse trabecular pattern and marked cortical rarefaction (Fig. 6D) was observed. Lateral and anterior bowing of femora and tibiae persisted. The epiphyses of the long bones were rather flat (knees) or small (hips). At the age of 6.3 years, radiological "disappearance" of the femoral heads occurred within a time interval of 3.5 months, with no clinical correlate. MRI examination of the pelvis at this time revealed signs of an inflammatory process of both hip joints and the left obturator internus muscle (see legend to Fig. 6F). Multiple fractures of the osteoporotic ribs were discovered at the age of 1.6 years, multiple metatarsal stress ("march") fractures at 3.5 years. The spine showed only minimal changes at the age of 8.2 years (mild shortening of the sagittal diameter of the vertebral bodies and moderate indentations of the endplates). At age 9 years, this patient is of normal intelligence and doing rather well but severely handicapped by short stature, joint contractures, impaired gait, and facial myotonia.

Bone pathology

Autopsy was performed in case 4 who died at the age of 3 months. In all growth plates examined (femur, tibia, fibula, rib, iliac crest), there was a regularly organized endochondral ossification contrasting with subsequent stages of primary and secondary ossification which were markedly disturbed and resulted in thick, irregular bone trabeculae (Fig. 5B).

Cartilage biochemistry

Cartilage samples obtained at autopsy (femoral head, case 4) or during surgery (talus, case 2) were minced and sequentially extracted with 4M guanidinium chloride and pepsin, as described [28]. The pepsin-extracted collagens were separated by sodium dodecyl sulphate-polyacrylamide gel electrophoresis together with control samples. The relative proportions and electrophoretic mobility of collagens II and XI was similar to that of control samples, making a significant structural change in these molecules unlikely.

Genetic analysis

To test whether the disorder cosegregated with the SJS locus on chromosome 1 p34-36 described recently by Nicole et al. [19], DNA from the two sibs (cases 4 and 5) with neonatal-onset SJS and their unaffected and presumed non-consanguineous parents was amplified by the polymerase chain reaction using one unlabelled and one fluorescein-labelled marker, and products were denatured and analysed on a Pharmacia ALF sequencer. Five markers were informative (in telomere-to-centromere order: D1S199, AFM343za9, D1S478, D1S482, D1S234). The resulting haplotypes are shown in Fig. 7. The girl had inherited an original paternal haplotype, while the boy had inherited a haplotype produced by paternal recombi-

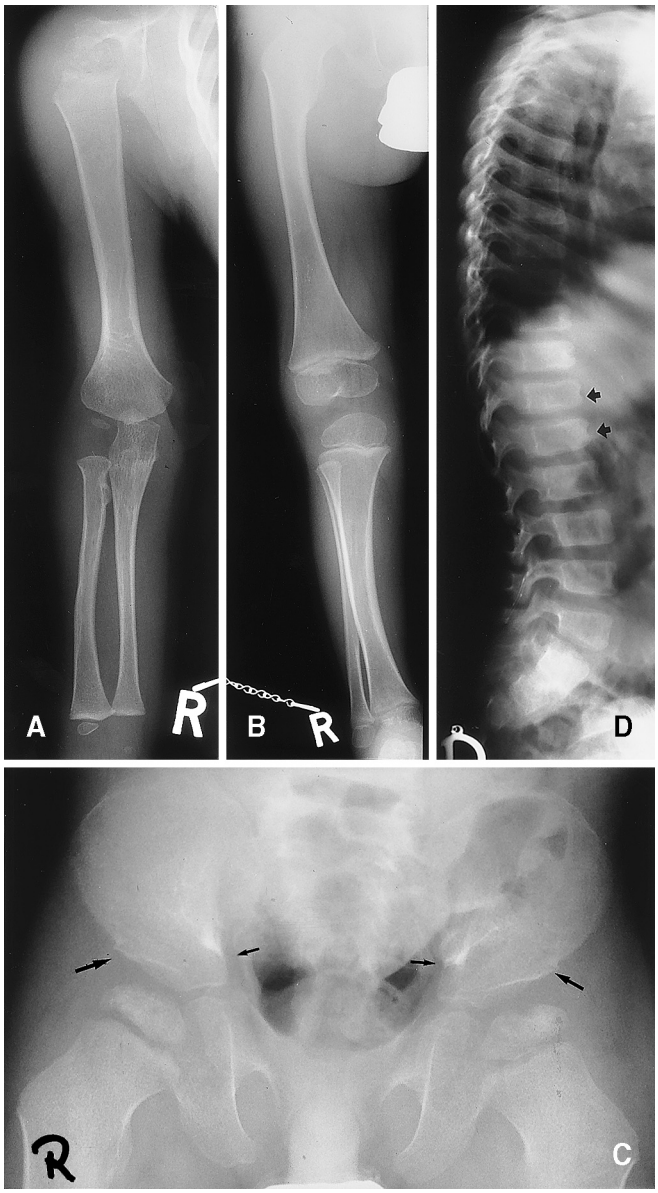


Fig. 2 A–D. Case 1 at the age of 2.3 years (**A**) Right arm: moderately widened metaphyses of humerus (**B**) Right leg: moderately enlarged epiphyses of knee; mild bowing of tibia; osteoporosis (**C**) Pelvis with narrow iliac wings, narrow, sclerotic sacrosciatic notch (*small arrows*); small bony spine (*large arrow*) at lateral end of acetabula, slight dysplasia of right acetabulum; irregular, small, partially defective femoral heads; wide ischium; osteoporosis (**D**) Lateral spine: mild flattening of lower thoracic and upper lumbar vertebral bodies, anterior scallopping (*arrowheads*)

nation between D1S478 and D1S482; each sib had inherited a different haplotype from the mother. Assuming linkage to the SJS locus on chromosome 1p34-36, which lies between markers D1S478 and D1S482 [10], in the maternal haplotype transmitted to one of the children double recombination should have occurred between D1S478 and D1S482. Since the genetic distance between these markers is approx. 4 cM [11], double recombination would be expected to occur with probabilities of 0.0016 (1.6/1000) for each meiosis. Thus, these markers give odds of approx. 600:1 against linkage to 1p34-36 in this family. The identification of new markers in the region will allow more precise calculations.

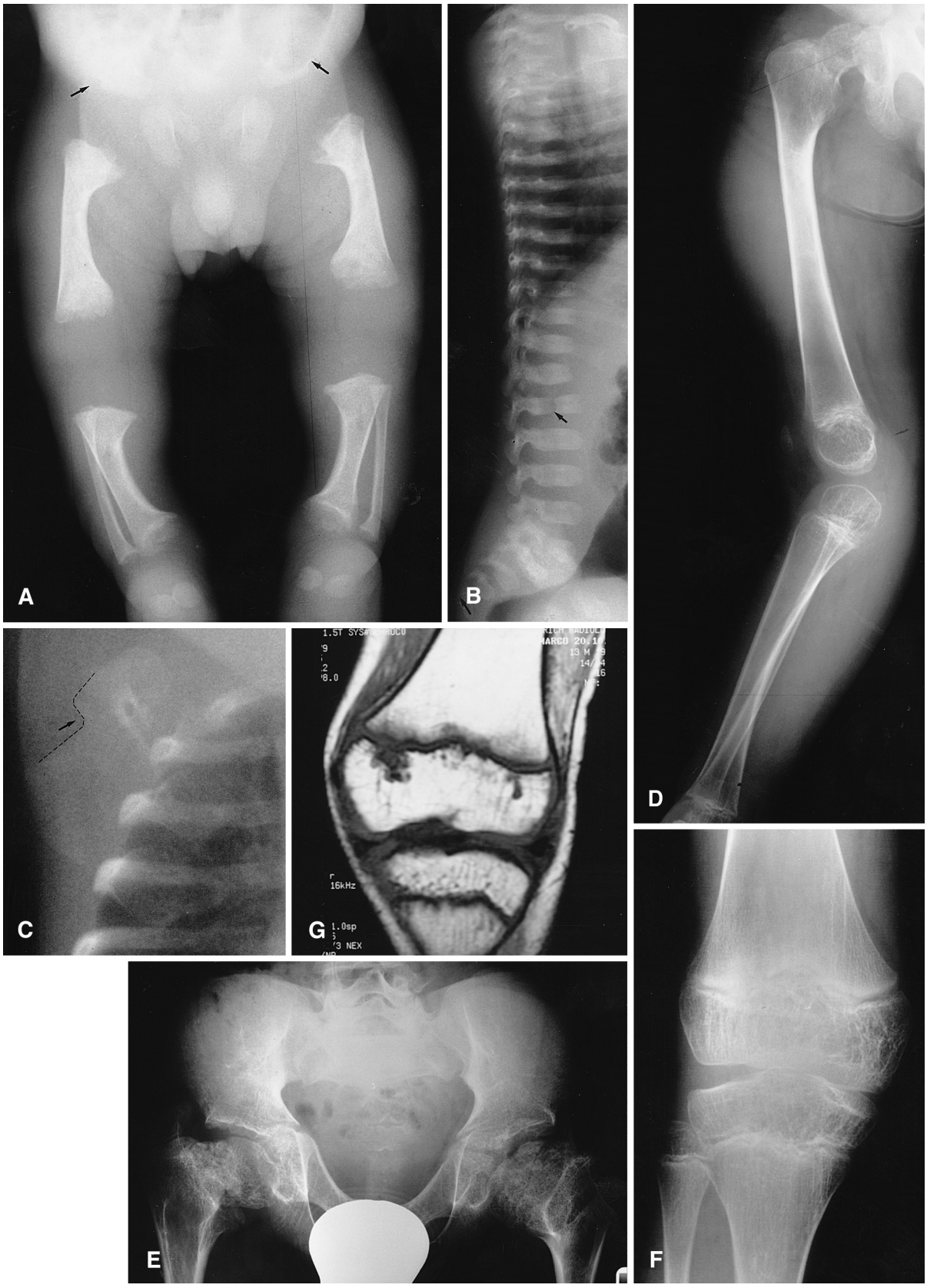
Discussion

The SJS (McK 255800) is defined by Aberfeld et al. [1] as "myotonia, dwarfism, diffuse bone disease and unusual ocular and facial anormalities". All our cases fulfill these criteria in spite of the fact that they have quite different clinical courses and radiological changes. A review of reports in the literature confirms that what has been called SJS ranges from relatively mild myotonia with subtle radiological signs to severe neonatal myotonia with contractures, evident bone dysplasia, and death in infancy. The two main diagnostic criteria, myotonia and skeletal changes, appear to be heterogeneous in themselves and will be commented upon below. To further complicate the picture, several other features, such as mental retardation or immunodeficiency, have been sporadically associated with SJS: these will not be commented upon here.

Neuromuscular findings in SJS

Clinical or neurophysiological evidence of myotonia is required for the diagnosis of SJS, but a myotonic EMG pattern is not specific for this diagnosis (for discussion see [25]). In some patients in the literature (as in our cases 1–3) myotonia was noticed during childhood (often because of characteristic facial changes), while in other patients contractures and microstomia were noticed at birth indicating prenatal onset of myotonia. Most cases (including the original cases [1, 24] described as having "myopathy") had firm but hypotrophic muscles, while some patients have hypertrophic muscles [7; our case 1]. In most SJS cases studied in this respect, myotonia was not influenced by the application of curare, but in others myotonic discharges were suppressed by curare (four cases from the literature [5, 9, 27] and our case 2), indicating neurogenic rather than myogenic myotonia. These discrepancies might suggest heterogeneity within SJS [5, 10]. Some patients with myotonia reported as SJS, particularly when dominantly inherited [21], may in reality have sodium-channel myotonia, caused by dominant mutations in the sodium-channel gene SCN4 [22, 25].

Fig. 3 A–G Case 2. A–C, newborn age (**A**) pelvis, lower extremities: Kniest-like appearance of femora and tibiae, supra-acetabular notch (*arrows*) (**B**) lateral spine: coronal cleft L 2 (*arrow*), coccyx not ossified (*long arrow*); (**C**) scapela: prominent glanoid process (arrow), round inferior angle, flared ends of ribs. (**D**) age 6 years. Right leg: external rotation (see Fig. 1a) with retrocurvation of knee; small femoral head; bulbous epiphyses of knee; osteoporosis (**E**) age 14 years. iliac wings now narrow; femoral heads moderately flattened, necks shortened and rotated with irregular structure and varus deformity; postoperative changes right side. (**F**) age 14 years. Right knee; rather large epiphyses, slightly flaring metaphyses; osteoporosis (**G**) age 13.5 years. MRI (T1 weighted coronal view) of left knee. Irregular physis with cartilage remnants within the adjacent epiphysis


A
B
C
D
E
F
G

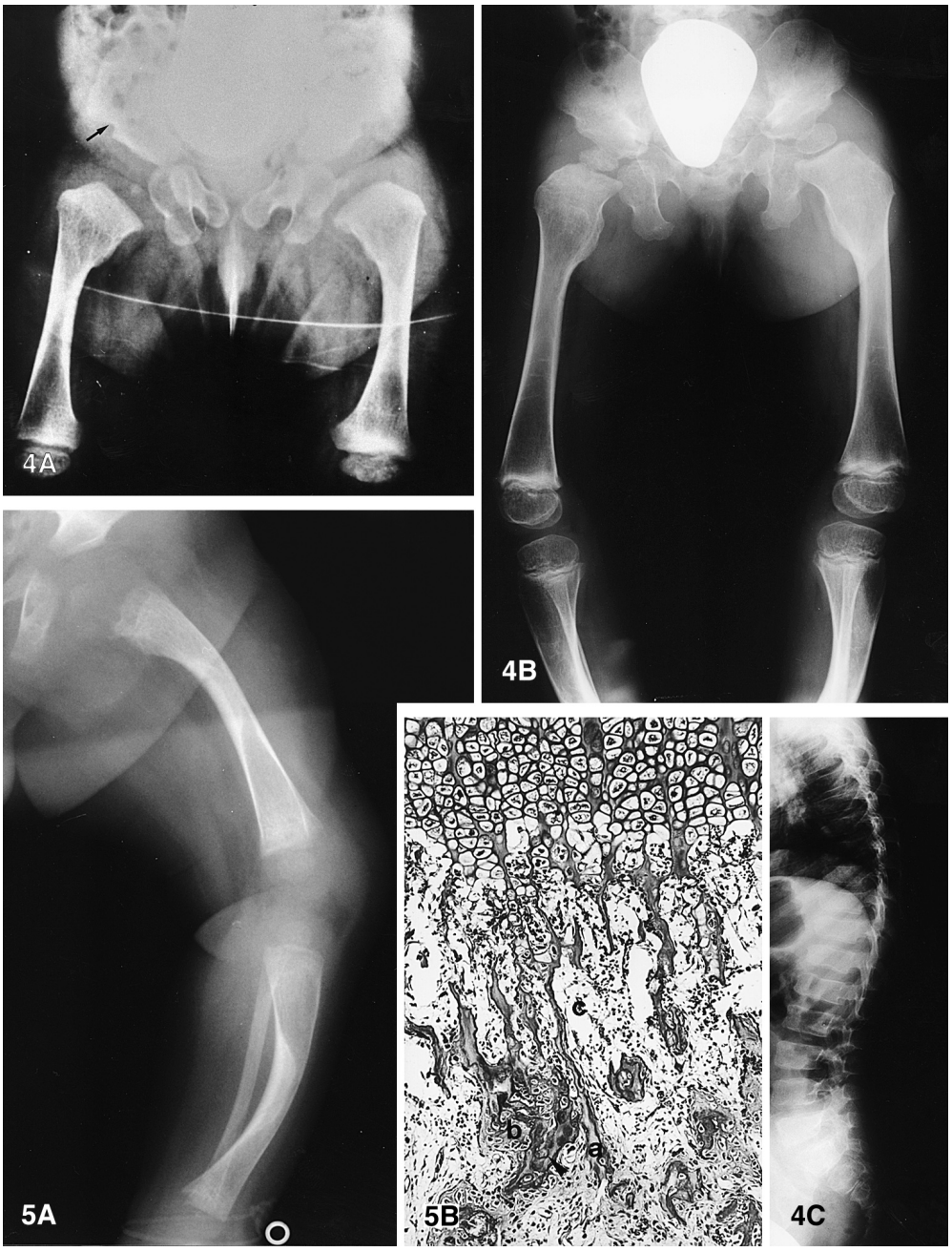


Fig. 4 A–C Case 3 (**A**) age 4 months. Pelvis, femora very similar to Fig. 2a; identical "notch" (*arrow*). The ischiopubic synchondrosis is wide (**B**) age 5 years. Small femoral heads (right < left); dysplastic acetabula; the ischiopubic synchondrosis remains unusually wide; moderately enlarged epiphyses at knee; anterior bowing of tibiae; osteoporosis (**C**) age 5 years. Lateral spine: moderate platyspondyly

Fig. 5 A, B Case 4, age 3 months (**A**) Left leg externally rotated; anterior (and lateral) bowing, mild undertubulation of metaphyses at knee; proximal femoral metaphysis irregular, osteoporosis (**B**) Proximal growth plate of left femur, H&E × 100. Irregular broad anastomosing bony trabeculae contain small remnants of cartilaginous matrix (**A**) but also groups of frankly necrotic chondrocytes (*arrowhead*). They are surrounded by fibrin and irregularly deposited osteoid (**B**). The loose primary bone marrow is oedematous and focally haemorrhagic. (**C**) Endochondral ossification is regular

Variability of skeletal radiological changes in SJS

Analysis of the skeletal findings in the SJS was hampered by the very limited documentation in the literature: only 35 of the 80 cases reviewed were illustrated, mostly with scanty radiographs, and longitudinal studies were lacking in most cases.

Secondary bone changes in SJS

Abnormal muscle tone can produce mild secondary skeletal changes, as suggested by Schwartz and Jampel and by others [17, 18, 24], and thus not be the primary expression of a bone dysplasia. Skeletal changes can also be observed in the dominantly inherited Freeman-Sheldon "whistling face" syndrome (McK 193700) and have been explained by "myofunctional engineering of osseous structures" [20, 23] i.e., bone remodelling because of abnormal muscle traction. The skeletal changes which may be produced by myotonia are listed in Table 2. Separating these secondary changes, which may develop over an extended time period, from true bone dysplasia can be difficult, as already remarked by Aberfeld and colleagues [1].

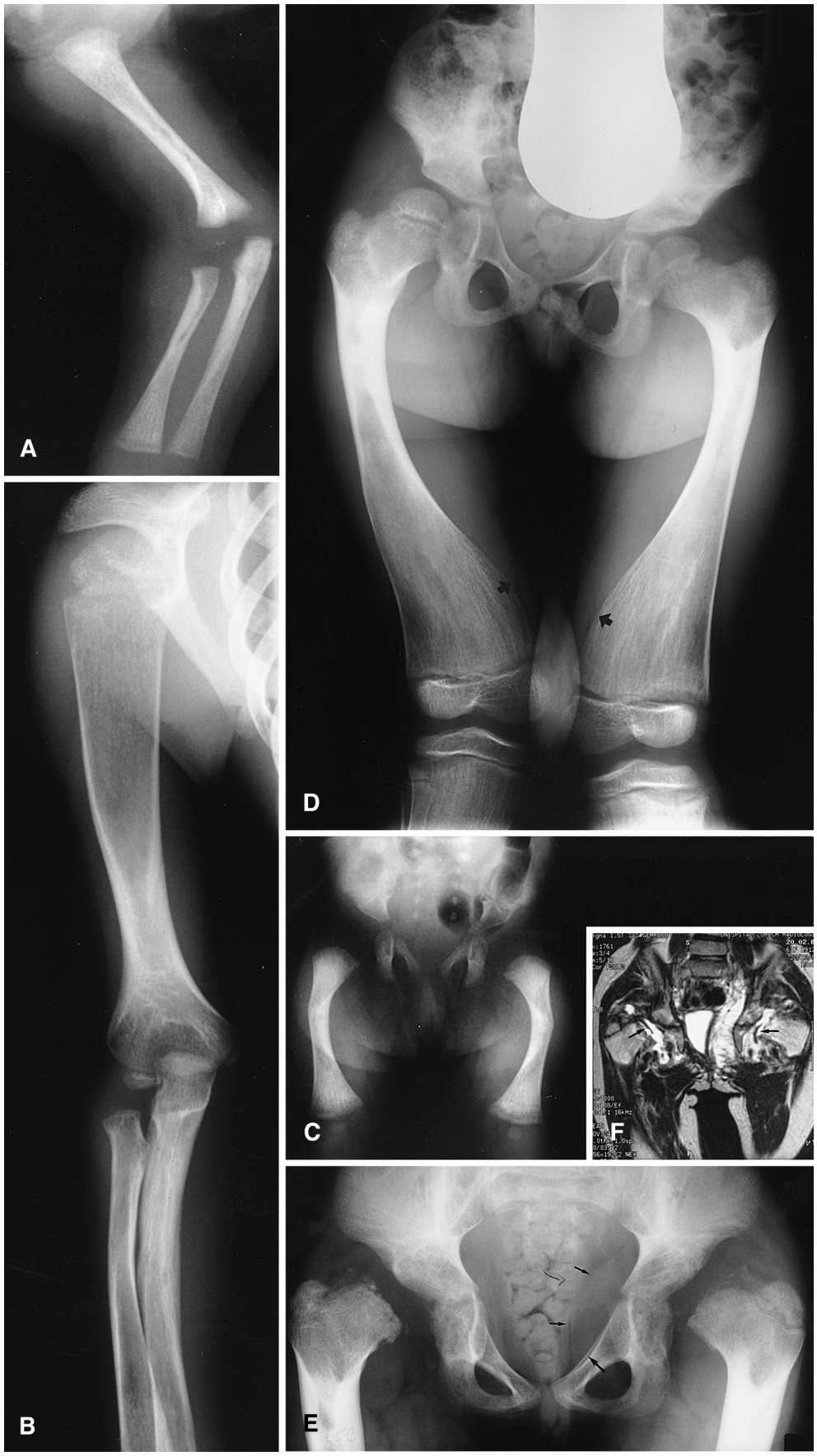


Fig. 6A–F Case 5 (**A**) Age 2 weeks. Right arm ''band'' of metaphyseal translucency in distal radius and ulna. Incipient undertubulation of long bones (**B**) age 6.5 years. Undertubulation of long bones and osteoporosis (**C**) Newborn age. Flared iliac wings; the femora are bowed and shortened and show some metaphyseal flare, but are not dumbbell shaped; ''bands'' as in *a* (**D**) age 6.3 years. Crura vara and genua valga; rather small, but well rounded femoral heads, flat epiphysis of the knee with undertubulation of metaphyses; streaky osteoporosis with radiological absence of cortex (*arrow*) (**E**) age 6.8 years (6 months later !). Complete disappearance of femoral heads; soft tissue masses (*arrows*); periosteal reaction (*large arrow*) (**F**) MRI (T2-weighted coronal view) of pelvis 3 weeks later. Diffuse hyperintensive swelling (oedema) of left lateral pelvic wall, deforming the wall of the urinary bladder; proximal femoral epiphyses have disappeared completely; hyperintense effusion and pannus formation in both hip joints; linear structures of low-intensity, probably representing cartilage residues (arrows).

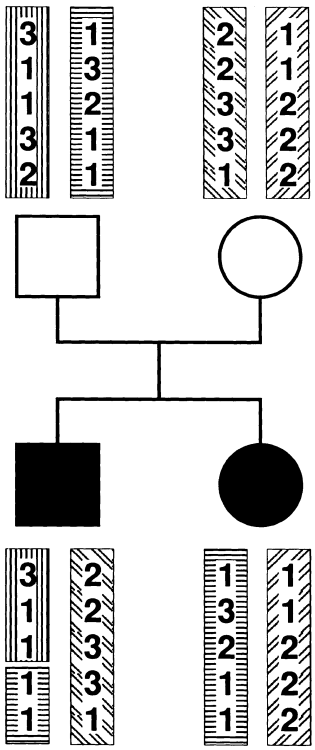


Fig. 7 Pedigree of the sibs (cases 4 and 5) affected by SJS type 2. Haplotypes composed of alleles for markers at chromosomal region 1p34-36 (D1S199, AFM343za9, D1S478, D1S482 and D1S234) are shown. The SJS locus described by Nicole et al. [19] and Fontaine et al. [10] lies between D1S478 and D1S482. See the text for further explanations

Table 2 Skeletal and articular findings in SJS probably secondary to myopathy

Cranial:	Flat face, hypognatia
Chest:	Pectus excavatum or carinatum
Long bones:	Bowing, external rotation of femora, coxa vara or valga, dysplasia or luxation of hips, retrocurvation of knees
Feet:	Talipes valgus or planus
Joints:	Contractures, "arthrogryposis"
General:	Osteoporosis

Primary bone dysplasias in SJS

The majority of cases have more distinct bone changes suggestive of a primary bone dysplasia. These changes are often observed before the clinical onset of myotonia. However, among these cases there is heterogeneity both in the severity and in the pattern of bone dysplasia. We tentatively delineate three types, the distinctive features of which are presented below and summarized in Table 3, but further heterogeneity may exist.

SJS type 1A: childhood onset, "classical" type (Figs. 1B, 2)

Radiological changes in childhood include moderate flaring of the metaphyses of the long bones, moderately enlarged epiphyses at the knees, progressive dysplasia of femoral heads, narrow pelvis and moderate platyspondyly, and osteoporosis. Additional secondary changes (e.g., pectus deformity) may be present. The diagnosis is usually made in childhood, often when a myotonic face with blepharospasmus or blepharophimosis and microstomia with pursed lips is recognized. Because the diagnosis is made relatively late, it is not known whether bone dysplasia is already present at birth. Examples of this type of SJS are the two siblings reported by Catel in 1951 [8], a patient described as "spondylo-epi-metaphyseal dysplasia with myotonia" [14], our case 1, and probably the sibs originally reported by Schwartz and Jampel [24] and by Aberfeld et al. [1].

SJS type 1B: neonatal onset with Kniest-like bone dysplasia in infancy (Figs. 1A, 3, 4)

Findings are in general more marked than in type 1A. Bone dysplasia is present at birth, although myotonia may be recognized only later (as in our cases 2 and 3). The long bones are shortened, the femora are dumbbell-shaped in infancy, the epiphyses of the long bones are rather large during childhood. With time, the femoral heads become dysplastic and the metaphyses become mildly to moderately widened. There is variable flattening of vertebral bodies, and coronal clefts are frequently observed in infancy. The configuration of the

Table 3 Proposed classification of the Schwartz-Jampel Syndrome

	Type 1A	Type 1B	Type 2
Usual time of manifestation	*Myotonia*: early childhood *Bone dysplasia*: childhood	*Myotonia*: infancy or childhood *Bone dysplasia: birth*	*Myotonia*: birth *Bone dysplasia*: birth
Leading radiological findings	Mild epi-metaphyseal dysplasia with enlarged epiphyses at knees	*Infancy*: Short-limbed dysplasia with dumbbell-shaped femora (Kniest dysplasia-like) *Childhood*: spondylo-epi-metaphyseal dysplasia	*Infancy*: short-limbed dysplasia with bowing of legs *Childhood*: Pyle disease-like undertubulation of long bones
Spine	Mild platyspondyly	Moderate platyspondyly, coronal clefts	Not characteristic
Pelvis	Narrow sciatic notch	Some flaring of iliac wings; presence of supra-acetabular notch	Not characteristic
Epiphyses	Moderately enlarged at knees and other long bones	Moderately enlarged at knees	Flattened at knees

Note: Osteoporosis and some degree of epiphyseal dysplasia can be seen in all three types

pelvis is quite characteristic with flared iliac wings, supra-acetabular lateral notches, and a wide ischium. Beyond infancy, reduced stature is invariably present. The radiological findings in later childhood show a pattern similar to that seen in type 1A. It is possible that types 1A and 1B are the childhood variant and the infantile variant of the same disease. Type 1B is exemplified by the patient of Calzolari et al. [6], the two severe cases of Horan and Beighton [12] (included in the genetic study of Nicole et al. [19]), our cases 2 and 3, and probably two siblings with "pursed lips" and a "Kniest-like" radiological appearance without mention of myotonia [4].

SJS type 2: neonatal onset with Pyle disease-like bone dysplasia (Figs. 5 and 6)

This type, apparently more severe, is illustrated by our two siblings (cases 4 and 5). In one sib, limb bowing and reduced fetal movements were seen by ultrasound before birth [13]. At birth, there was a short-limbed dysplasia with marked bowing of long bones. One of the sibs deceased at age 3 months; in the surviving sib, there was progression during childhood to spectacular undertubulation of the metaphyses, marked osteoporosis, but only minimal vertebral involvement. The pattern of bone changes is distinct from that seen in types 1A and 1B, and the evidence suggesting no linkage to the SJS locus on chromosome 1p36-34 supports the separation of this form from types 1A and 1B. No examples of this radiological pattern were found in the literature but the radiological appearance of several of the cases with neonatal SJS reported by Al-Gazali et al. [2, 3] are similar to those of our sibs with SJS type 2 in the neonatal period. Early death was quite frequent in that series and radiological follow up is not available. Since those patients originate from a distinct ethnic group (Omani) and thus may be genetically homogeneous, it will be interesting to see whether SJS in that population maps to chromosome 1p36-34 or not (see below).

The molecular basis of SJS

Several families with multiple sibs born to unaffected consanguineous parents have been reported, strongly suggesting recessive inheritance of SJS. Families with "dominant SJS" [21] may represent sodium-channel mutations or other forms of myotonia rather than SJS (see above), and dominant inheritance probably excludes the diagnosis of SJS. The first important step in the unraveling of the molecular basis of autosomal recessive SJS has been accomplished by Nicole et al. [19], who studied five families with SJS and found evidence for linkage to chromosome 1p36.1-p34. Quite recently, Fontaine and coworkers [10] refined the mapping of the SJS locus by studying eight more families with phenotypes ranging from very mild to severe and thus probably encompassing types 1A and 1B: no evidence for a second locus was observed. Experience shows that chondrodysplasias of quite different severity may be caused by mutations at a same locus [16, 26], and it is conceivable that SJS type 1A and 1B may be caused by allelic mutations resulting in childhood onset with mild bone changes or neonatal onset with more marked bone dysplasia. Eventually, gene cloning and mutation analysis will allow to look for genotype-phenotype correlations. On the other hand, DNA studies have brought preliminary evidence against linkage to the SJS locus on 1p36.1-34 in our set of sibs (cases 4 and 5) who appeared to have – even before the results of the DNA studies were available – a distinct disorder with prenatal onset of myotonia and unique radiological findings, which we have tentatively classified as SJS type 2. Understanding the heterogeneity in SJS will ultimately rely on molecular pathology. The proposed clinico-radiological classification may help characterizing patients and establishing genotype-phenotype correlations.

Acknowledgements We thank Dr. W. Meyer (Wil) for his valuable information and radiographs of case 2; Prof. B. Hadorn and PD Dr. K. Schneider (von Haunersches Kinderspital, University of Munich) for their help in collecting the data of case 1; Dr. B. Reitter (Children's Hospital, University of Mainz) for the neurological examination and the EMG, and Dr. M. Roubicek (formerly visiting professor, Children's Hospital, University of Mainz) for his valuable studies on case 3; Dr. L. I. Al-Gazali (UAE University, Al Ain) for lending us original radiographs for inspection [2]; Prof. P. Beighton (Cape Town University of South Africa) for copies of radiographs and clinical informations [12]; and Prof. P. Maroteaux (Hôpital Necker, Paris) for a critical review of the manuscript. This study was supported by the Swiss National Science Foundation (SNF grants no. 32-45401.95 and 32-42198.94 and the Julius Klans-Stiftung).

References

1. Aberfeld DC, Hinterbuchner LP, Schneider M (1965) Myotonia, dwarfism, diffuse bone disease and unusual ocular and facial abnormalities (a new syndrome). Brain 88:313–322
2. Al-Gazali LI (1993) The Schwartz-Jampel syndrome. Clin Dysmorphol 2:47–54
3. Al-Gazali LI Varghese M, Varady E, AI Talabani J, Scorer J, Bakalinova D (1996) Neonatal Schwartz-Jampel syndrome: a common autosomal recessive syndrome in the United Arab Emirates. J Med Genet 33:203–211
4. Burton BK, Sumner T, Langer LO, Rimoin DL, Adomian GE, Lachman RS, Nocastro JF, Kelly DL, Weaver RG (1986) A new skeletal dysplasia: Clinical, radiologic, and pathologic findings. J Pediatr 109:642–648
5. Cadilhac J, Baldet P, Greze J, Duday H (1975) EMG studies of two family cases of the Schwartz and Jampel syndrome. Electromyogr Clin Neurophysiol 15:5–12
6. Calzolari C, Vichi GF, Pacini M. Giovannucci ML, Marconi G, Bani Sacchi T, Granelli L (1982) Sindrome di Schwartz-Jampel con singolari alterzioni scheletriche. Riv Ital Pediatr 8:265–277
7. Cao A, Cianchetti C, Calisti L, De Virgilis S, Ferreli A, Tangheroni W (1978) Schwartz-Jampel syndrome. Clinical, electrophysiological and histopathological study of a severe variant. J Neurol Sci 335:175–187
8. Catel W (1951) Differentialdiagnostische Symptomatologie von Krankheiten des Kindesalters, 2nd edn. Georg Thieme, Stuttgart, pp 48–52
9. Edwards WC, Root AW (1982) Chondrodystrophic myotonia (Schwartz-Jampel syndrome): report of a new case and follow

up of patients initially reported in 1969. Am J Med Genet 13:51–56.
10. Fontaine B, Nicole S, Topaloglu H, Ben-Hamida C, Beighton P, Spaans F, Cantu JMA, Bakouri S, Romero N, Ricker K, Barros-Nunez P, Ponsot G, Ben-Hamida M, Weissenbach J, Hentati F, Lehmann-Horn F (1996) Recessive Schwartz-Jampel syndrome (SJS) - confirmation of linkage to chromosome 1p, evidence of genetic homogeneity and reduction of the SJS locus to a 3-cm interval. Hum Genet 98:380–385
11. Gyapay G, Morissette J, Vignal A, Dib C, Fizames C, Millasseau P, Marc S, Bernardi G, Lathrop M, Weissenbach J (1994) The 1993–1994 Généthon human genetic linkage map. Nature Genet 7:246–339
12. Horan F, Beighton P (1975) Orthopaedic aspects of the Schwartz syndrome. J Bone Joint Surg 57 [Am]:542–544
13. Hunziker UA, Savoldelli G, Boltshauser E, Giedion A, Schinzel A (1989) Prenatal diagnosis of Schwartz-Jampel syndrome with early manifestation. Prenat Diagn 9:127–131
14. Kozlowski K, Wise G (1974) Spondylo-epi-metaphyseal dysplasia with myotonia. A radiographic study (Catel-Hempel syndrome, Schwartz-Jampel syndrome, Aberfeld syndrome, chondrodystrophic myotonia). Radiol Diagn (Berl.) 6:817–824
15. Lachman RS, Rimoin DL, Hollister DW, Dorst JP, Siggers DC, McAlister W, Kaufman RL, Langer LO (1975) The Kniest syndrome. Am J Radiol 123:805–814
16. McKusick VA, Amberger JS, Francomano CA (1996) Progress in medical genetics: map-based gene discovery and the molecular pathology of skeletal dysplasias. Am J Med Genet 63:98–105
17. Mereu TR, Porter IH, Hug G (1969) Myotonia, shortness of stature and hip dysplasia. Schwartz-Jampel syndrome. Am J Dis Child 117:470–478
18. Milachowski K, Keyl W, Witt TN (1982) Das Schwartz-Jampel-Syndrom. Orthopädische und neurologische Probleme der chondrodystrophen Myotonie. Z Orthop 120:657–661
19. Nicole S, Ben Hamida C, Beighton P, Bakouri S, Belai S, Romero N, Viljoen D, Ponsot G, Sammoud A, Weissenbach J (1995) Localization of the Schwartz-Jampel syndrome (SJS) locus to chromosome 1p34–p36.1 by homozygosity mapping. Hum Mol Gen 4:1633–1636
20. O'Connell DJ, Hall CM (1977) Cranio-carpo-tarsal dysplasia, Radiology 123:719–722
21. Pascuzzi RM, Gratianne R, Azzarelli B, Kincaid JC (1990) Schwartz-Jampel syndrome with dominant inheritance. Muscle Nerve 13:1152–1163
22. Rüdel R, Ricker K, Lehmann-Horn F (1993) Genotype-phenotype correlations in human skeletal muscle sodium channel diseases. Arch Neurol 50:1241–1248
23. Sauk JJ, Delaney JR, Reaume C, Brandjord R, Witkop CJ (1974) Electromyography of oral-facial musculature in craniocarpaltarsal dysplasia (Freeman-Sheldon syndrome). Clin Genet 6:132–137
24. Schwartz O, Jampel RS (1962) Congenital blepharophimosis associated with a unique generalized myopathy. Arch Ophthalmol 68:52–57
25. Spaans F, Theunissen P, Reekers AD, Smit L, Veldman H (1990) Schwartz-Jampel syndrome: I. Clinical, eletromyographic and histologic studies. Muscle Nerve 13:516–527
26. Superti-Furga A, Rossi A, Steinmann B, Gitzelmann R (1996) A chondrodysplasia family produced by mutations in the diastrophic dysplasia sulfate transporter gene: genotype/phenotype correlations. Am J Med Genet 63:144–147
27. Taylor RG, Layzer RB, David HS, Fowler WM (1972) Continuous muscle fiber activity in the Schwartz-Jampel syndrome. Electroencephalogr Clin Neurophysiol 33:479–509
28. Winterpacht A, Superti-Furga A, Schwarze U, Stöss H, Steinmann B, Spranger J, Zabel B (1996) The deletion of six amino acids at the C-terminus of the α1(II) chain causes overmodification of type II and type XI collagen: further evidence for the association between small deletions in COL2A1 and Kniest dysplasia. J Med Genet 33:649–654