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Genetic Heterogeneity in Spondylo- epi- metaphyseal Dysplasias: A Clinical and Radiological Study

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ABSTRACT

Introduction: Spondylo-epi-metaphyseal dysplasias (SEMD) are a heterogeneous group of skeletal disorders characterized by defective growth and modeling of the spine and long bones. Different types are described in the literature. Accurate classification of SEMDs is essential for proper genetic counseling.

Patients and Methods: This study included 20 cases of SEMDs diagnosed by clinical and radiological findings. Cases were classified based on additional associated clinical and/or radiological features into 7 subtypes. Different subtypes were discussed with review of the literature.

Results: The study illustrated the heterogeneity of SEMDs and emphasized the importance of detailed and meticulous clinical genetic and biochemical evaluation in addition to comprehensive radiological investigations for such group of disorders. It also recommends further molecular studies to identify the molecular bases of the different types.

Key Words:

Spondyloepimetaphyseal dysplasias, Genetic heterogeneity, Dyggve-Melchior-Clausen dysplasia, Glycoaminoglycans.

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INTRODUCTION

Spondylo-epi-metaphyseal dysplasias (SEMD) are a clinically and genetically heterogeneous group of skeletal disorders characterized by defective growth and modeling of the spine and long bones. In SEMD, disturbed growth can be recognized by abnormal radiographic findings within the epiphyses of long bones, the adjacent metaphyses and the vertebral bodies.

By reviewing the OnLine Mendelian Inheritance in Man[1] and London Medical Databases[2] more than 15 subtypes of SEMD were reported with different patterns of inheritance and associated findings.

Mutations in different genes have been discovered in some types, in the latest International Nosology

of Skeletal Dysplasias based on a molecular-pathogenetic classification, SEMDs were subgrouped under type II collagenopathies, type XI collagenopathies and a separate group with yet unknown or different molecular causes.[3]

Although classification of SEMD is nosologically difficult, differentiation between subtypes is important as the mode of inheritance, development and prognosis of these disorders is different.

In this study we performed detailed clinical and radiological studies of 20 Egyptian patients with SEMD. Cases were subclassified according to the characteristic clinical or radiological findings with review of the literature and discussion of the probable underlying molecular defects.

This study aimed at the accurate diagnosis, classification and proper genetic counseling of referred cases with SEMD. It also aimed at illustrating the genetic heterogeneity of this group of skeletal disorders.

PATIENTS AND METHODS

The study included 20 Egyptian patients (9 males, 11 females) from 15 unrelated families. Patients were referred to the Limb and Skeletal Anomaly Clinic, Medical Services Unit, National Research Centre either due to short stature, skeletal abnormalities or associated mental retardation. Their ages at presentation ranged from 1 year to 28 years.

All cases were subjected to detailed history taking, three generation family pedigree analysis, complete physical examination including phenotype analysis, orodental manifestations, anthropometric measurements (Height, weight, head circumference, arm span, sitting height and upper/lower U/L segment ratio) and skeletal survey. Quantitative estimation of glycosamino-glycanes (GAGs) in urine and two dimensional electrophoresis of the the GAGs were performed to all studied patients to exclude the possibility of mucopolysaccharidosis (MPS).[4,5] Measurement α-L-Iduronidase activity and galactose-6-sulphatase activity were done in suspected cases to exclude Hurler and Morquio diseases (MPS type I & MPS type IVA), respectively. Enzymatic assay was carried out according to the methods described by Kresse et al.[6] Ophthalmologic examination, hearing assessment, IQ, echocardiography, abdominopelvic ultrasound, serum level of calcium, phosphorus, alkaline phosphatase and bone densitometry (DEXA) were carried out whenever indicated.

RESULTS

Patients were diagnosed as having SEMD by the presence of short stature associated with radiological abnormalities of vertebrae, epiphyses and metaphyses of long bones and after the biochemical exclusion of MPS. According to additional characteristic clinical or radiological findings cases were classified into 7 subtypes with examples of illustrative figures for each subtype. Figure (1) includes the pedigrees of familial cases.

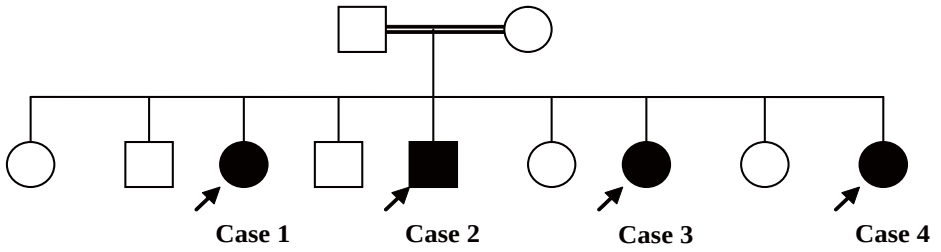

Fig. 1a: Family Pedigree of cases 1-4 with DMC syndrome

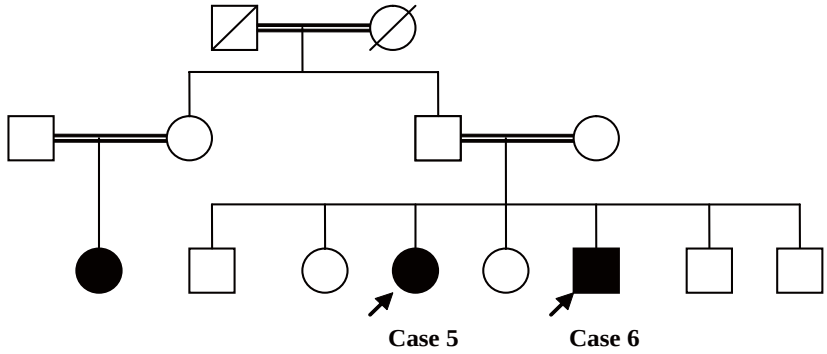

Fig. 1b: Family Pedigree of cases 5 &, 6 with DMC syndrome

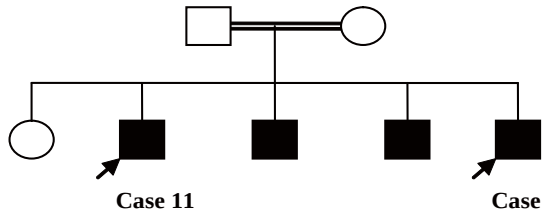

Fig. 1c: Family Pedigree of cases 11 & 12 with X-linked SEMD and MR

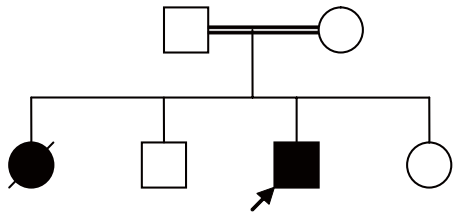

Fig. 1d: Family Pedigree of case 13 with SEMDJL

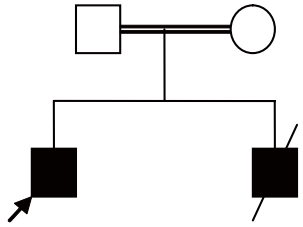

Fig. 1e: Family Pedigree of case 14 with SEMDJL

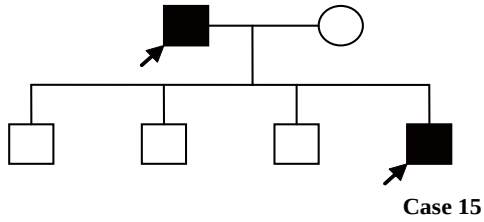

Fig. 1f: Family Pedigree of case 15 with SEMDJL

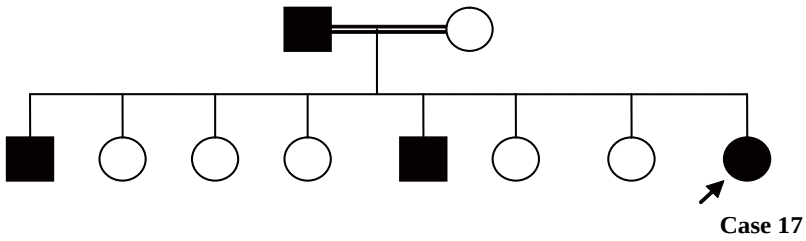

Fig. 1g: Family Pedigree of case 17 with SEMD-Strudwick type

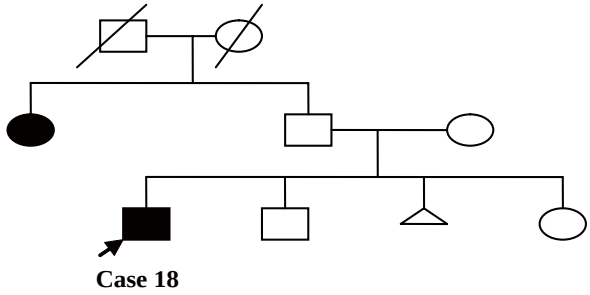

Fig. 1h: Family Pedigree of case 18 with SEMD-Strudwick type

Fig. 1: Pedigrees of familial cases with SEMD. Fig. 1a: Family pedigree of cases 1-4 with DMC syndrome. Fig. 1b: Family pedigree of cases 5 & 6 with DMC syndrome. Fig. 1c: Family pedigree of cases 11 & 12 with SEMD-XL with MR. Fig. 1d: Family pedigree of case 13 with SEMDJL. Fig. 1e: Family pedigree of case 14 with SEMDJL. Fig. 1f: Family pedigree of case 15 with SEMDJL. Fig. 1g: Family pedigree of case 17 with SEMD-Strudwick type. Fig. 1h: Family pedigree of case 18 with SEMD-Strudwick type.

Sub-type I: This included 9 patients (Cases 1-9) from 5 different families. All were the offspring of consanguineous parents. Family (1) included 4 affected sibs (1 male and 3 females), family (2) included 1 male and 1 female sibs (Cases 5, 6) with history of a similarly affected cousin, offspring of consanguineous parents, family (3) had an affected female (Case 7) with history of 2 similarly affected cousins, offspring of consanguineous parents, family 4 had an affected female (Case 8), while family 5 had an affected male (Case 9). Their heights were below normal (-3.7 to 7.1 SD) with decreased U/L segment ratio and their head circumferences were below normal (-3.1 to -5.9). The common characteristic features in this subtype included microcephaly, mental retardation and a characteristic lacy appearance of iliac bones. No corneal

clouding, hearing deficit, cardiac anomalies or organomegaly were detected in any case.

Table (1) summarizes the clinical and radiological data of cases 1-9. (figure 1a, b) shows the family pedigrees of cases 1-4 and cases 5 & 6 respectively.

Figures (2-6) are illustrative examples of the clinical and radiological findings in cases (1-9). Please note that the lace like appearance of iliac wings was clearly evident on the original X-ray films of the studied cases but was not so obvious in the reproduced photos in (Figures 4c, 5b, 6a).

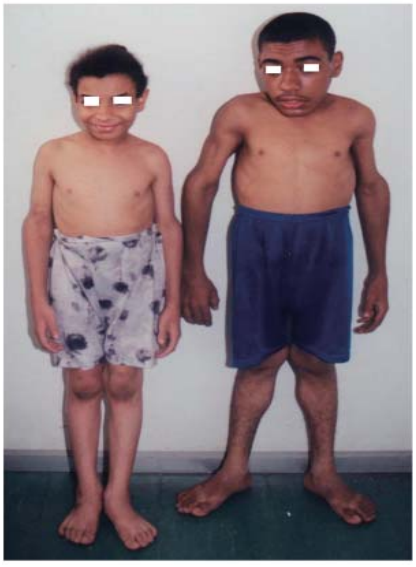

Fig. 2: Frontal view of cases 2 & 4 of family 1 with DMC syndrome at 23 and 13 years of age showing their clinical features.

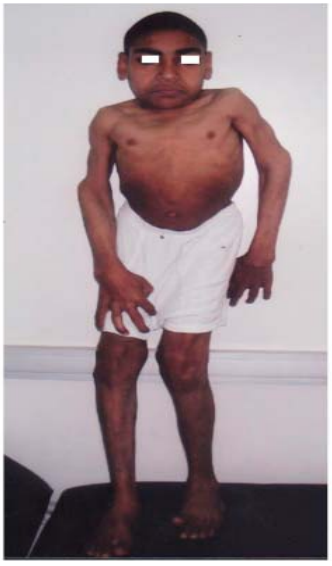

Fig. 3: Frontal view of case 6 with DMC syndrome at 14 years of age showing his clinical features.

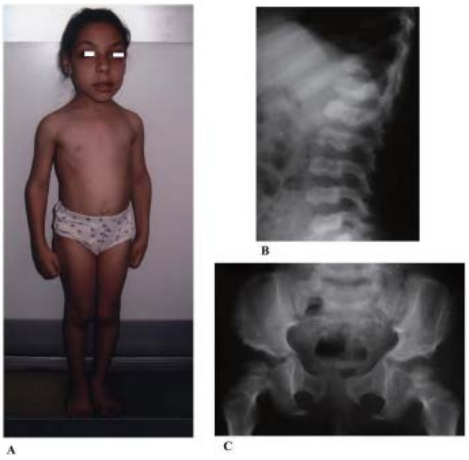

Fig. 4: Case 7 with DMC syndrome at 10 years and 4 months of age. Frontal view showing clinical features (A). X-ray (Lateral view) of thoraco-lumbar vertebrae showing platyspondyly with double constriction of lumbar vertebrae (B). X-ray of pelvis and long bones of lower limbs showing lace like appearance of iliac wings and mild epiphyseal and metaphyseal changes (C).

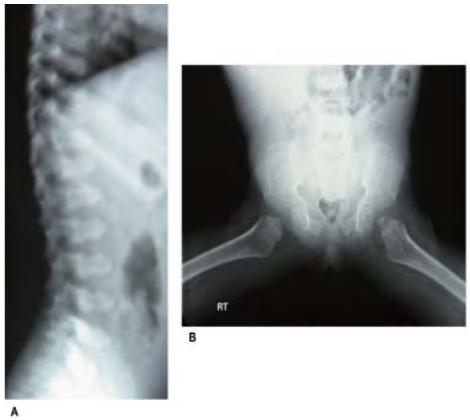

Fig. 5: Radiological findings in case 8 with DMC syndrome at 10 years of age. X-ray (Lateral view) of thoraco-lumbar vertebrae showing platyspondyly with double constriction of lumbar vertebrae (A). X-ray of pelvis showing narrow pelvis, hypoplastic femoral heads and lace like appearance of iliac wings (B).

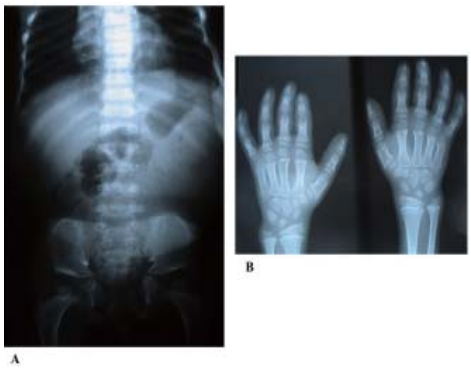

Fig. 6: X-ray (PA view) of thoracolumbar vertebrae, chest and pelvis in case 8 with DMC syndrome at 10 years of age showing flat vertebrae, thin ribs and lace like appearance of iliac bones (A). X-ray of both hands (PA view) showing short matacrpals and phalanges with broad metacarpal ends (B)

Although GAGs were elevated in urine in all 9 patients, MPS was excluded by electrophoresis of GAGs and normal activity of α-L-iduronidase and galactose-6-phosphatase enzymes.

Sub-type II: Case (10), a 13 years and 6 months old female patient, who presented with multiple skeletal anomalies and difficulty in walking. She is the offspring of first cousins parents. Pregnancy and delivery histories were irrelevant. Her height at examination was below normal (-6.4SD) with decreased U/L segment ratio while her head circumference was on the mean for her age. Developmental history was normal and IQ shows average intelligence. Clinical examination showed broad forehead, everted lower lip, prognathism, short trunk, short barrel shaped chest, kyphoscoliosis, fusiform fingers with broad metacarpophalangeal joints and bilateral overriding 3rd toes Figure (7A). Macroglossia, enamel hypoplasia and hypocalcification and amelogenesis imperfecta were noted by orodental examination. Chest, heart and abdomen were clinically free.

Table 1: Genetic, clinical & radiological data of subtype I (cases 1-9).

Case no.	Sex	Age (years)	Consan-guinity	Family History	Facial & dental manifestations	Other clinical features	Radiological findings	Others
Family 1 (Fig. 1a)								
Case 1	F	28	+	Similarly affected sibs	Narrow forehead, macrostomia, thick lips, simple ears with attached lobes, prominent premaxilla, macrognathia, lobulated tongue, high arched palate, and malocclusion.	**MR, microcephaly**, short neck, pigeon chest, hyperlordosis, broad metaphyses, clinodactyly of 5th fingers,	Platyspondyly, scoliosis, small epiphyses, broad metaphyses, narrow rounded pelvis with **lace like appearance of iliac crests.**	Limited extension of elbows, dysplastic nails. Generalized hirsutism. CT scan brain: Central & cortical brain atrophy.
Case 2 (Fig. 2)	M	23	+	Similarly affected sibs	Similar to case (1)	Similar to case (1)	Similar to case (1)	Dysplastic nails, dysarthric speech & stereotyped movements
Case 3	F	17	+	Similarly affected sibs	Similar to case (1)	Similar to case (1)	Similar to case (1)	Limited extension of elbows. CT scan brain: Central & cortical brain atrophy.
Case 4 (Fig. 2)	F	13	+	Similarly affected sibs	Similar to case (1)	Similar to case (1)	Similar to case (1)	-
Family 2 (Fig. 1b)								
Case 5	F	16	+	Similarly affected sib & cousin	Low hair line, narrow forehead, flat malar bone, thick eye brows, broad nose, long philtrum, macrostomia, prominent jaw, thick fissured lips, thick alveolar ridges, macrodontia.	**MR, microcephaly,** short neck, flaring of ribs, pectus carinatum, kyphoscoliosis, broad metaphyses, camptodactyly.	Platyspondyly, kyphoscoliosis, fragmented epiphyses, metaphyseal flaring, hypoplastic cetabullum, small iliac bone with **lacy appearance of iliac crests.**	Dysplastic nails. Generalized hirsutism.

cont.'

Case no.	Sex	Age (years)	Consan-guinity	Family History	Facial & dental manifestations	Other clinical features	Radiological findings	Others
Case 6 (Fig. 3)	M	14	+	Affected sib & cousin	Similar to case (5)	Similar to case (5)	Similar to case (5)	Bilateral pes cavus, short low inserted big toes.
Family 3								
Case 7 (Fig. 4 A)	F	10 4/12	+	Affected sib	Long face, long philtrum, macrostomia, macrognathia, thick lips, bifid tongue tip, high arched palate, macrodontia, crowding of teeth, prominent median palatine raphe.	**MR, microcephaly,** short neck, pectus carinatum, broad interphalngeal joints, brachydactyly.	Platyspondyly with double constriction of lumbar vertebrae (Fig. 4 B), mild epiphyseal and metaphyseal changes, **lace like appearance of iliac wings (Fig. 4 C).**	Hypoplastic nails.
Family 4								
Case 8	M	10 2/12	+	-	Triangular face, long nose, maxillary hypoplasia, thick upper labial frenum, high arched palate, bifid tongue tip, prominent median palatine raphe.	**MR, microcephaly,** short neck, pectus carinatum, scoliosis, brachydactyly, clinodactyly of 5th fingers, talipes equinovarus.	Platyspondyly, with double constriction of lumbar vertebrae (Fig 5 A), small epiphyses, irregular metaphyseal ends, narrow pelvis, **lace like appearance of iliac wings** (Fig. 5 B, 6 A). Metacarpals and phalanges are short with broad metaphyseal ends (Fig. 6 B).	Limitation of extension of interphalangeal joints.
Family 5								
Case 9	F	4 2/12	+	-	Narrow forehead, synophros, long philtrum, thick everted lips, highly attached labial frenum, macroglossia, geographic tongue.	**MR, microcephaly,** broad epiphyseal ends, pigeon chest, pectus carinatum, abdominal distension.	Platyspondyly, small epiphyses, fraying and eaten like metaphyseal ends, flat acetabulum and **lace like appearance of iliac bones.**	Incomplete extension of knees. Hirsutism on the back.

Skeletal survey revealed platyspondyly with central constriction of vertebral bodies, generalized abnormalities of epiphyses and metaphyses with generalized decreased bone density and lacy appearance of iliac crests Figure (7b & c). DEXA was normal at the spine with border line osteoporosis of the pelvis. Biochemical analysis showed an increased amount of GAGs in urine, while electrophoresis and enzyme activities were normal.

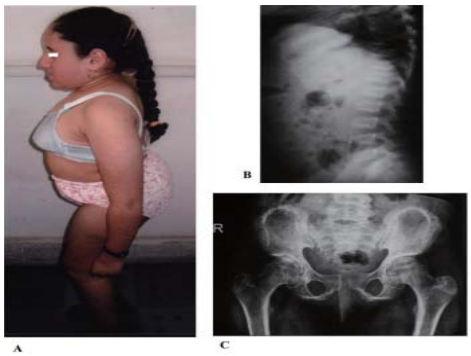

Fig. 7: Case 10 with SMC dysplasia at 13 years and 6 months of age. Lateral view showing the clinical features (A). X-ray (Lateral view) of lumbar vertebrae showing platyspondyly with central constriction of vertebral bodies (B). X-ray of pelvis showing the characteristic lace like appearance of iliac bones and the decreased bone density (C).

Subtype III: Comprised 2 male sibs (Cases 11, 12), offspring of second cousins parents. There was a history of 2 similarly affected brothers, who were not available for examination (Family pedigree figure 1c).

Case (11) presented at 16 years of age due to short stature, skeletal abnormalities and mental deterioration. The condition started at 3 years of age and was progressive. On examination, he was proportionately short with height below normal (-7.95 SD) and normal U/L segment ratio, microcephalic with a head circumference below normal (-3.0 SD), mental subnorma-lity, dysarthric speech, short neck, flaring of lower ribs, lumbar lordosis, diverication of recti, narrow pelvis and limited movements of interphalangeal joints. Facial features included narrow forehead, broad nose, thick lips and attached ear lobules. Dental examination revealed highly attached upper labial frenum and long uvula. Chest, heart and abdomen were clinically free.

Radiological examination of vertebrae, long and short bones revealed platyspondyly, small epiphyses, metaphyseal widening, dysplastic femoral heads and shallow acetabula with narrow pelvis. No irregularities or bony deposition on iliac bones were present. Computed tomography (CT) of the brain showed cortical brain atrophy and hypogenesis of corpus callosum. The patient was bedridden by 18 years of age.

Case (12): The younger brother of case (11). He presented at 7 years of age and had similar clinical and radiological manifestations like his brother. CT scan brain was normal. Pelvic ultrasound revealed hydronephrotic changes.

Figure (8) shows the clinical findings in cases (11, 12).

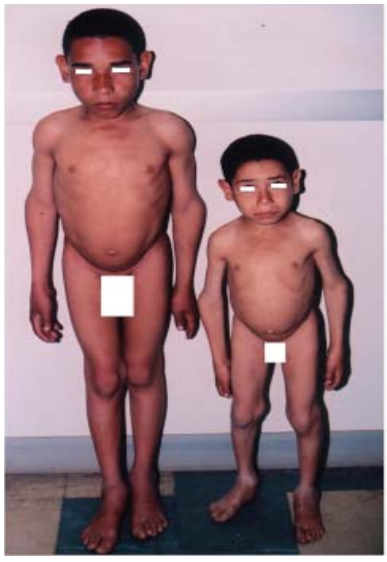

Fig. 8: Frontal view of cases 11 & 12 with SEMD-XL with MR at 16 and 7 years of age respectively showing the characteristic facial features.

Sub-type IV: Included 4 patients, 3 males and 1 female (Cases 13-16) All had marked hyperextensibility of interphalangeal joints and wrists. Cases (13, 14) were the offspring of consanguineous apparently normal parents. Case (13) had a history of similarly affected sister with cleft palate, who died from congenital heart disease (CHD) (Family pedigree figure 1d). Case (14) had a similarly affected male sib who died during the neonatal period from an associated CHD (Family pedigree figure 1e).

Case (15) is the offspring of non-consanguineous parents. His father is similarly affected (Family pedigree figure 1f). Both father and affected son had myopia. Clinical examination of the father showed sloping shoulders, pectus carinatum and bow legs. He also had hyperextensibility of interphalangeal joints and wrists and short hands and feet with brachydactyly of fingers & toes Figure (12a, b). Radiological examination of the father revealed oval shaped vertebrae with tongue like anterior projections and decreased intervertebral spaces (Figure 13a). Long and short bones showed dysplastic epiphyses, wide metaphyses, wide joint spaces and short broad metacarpals.

Case (16) presented at 14 years of age due to short stature. She is the offspring of non-consanguineous parents. Her paternal and maternal ages at her birth were 49 and 38 years, respectively.

Hearing assessment and clinical examination of chest, heart and abdomen were normal in all cases.

Table (2) presents the genetic, clinical and radiological data of cases (13-16). Figures (9, 10, 11, 12c, 13b, 14) are illustrative examples of the clinical and radiological findings in cases 13-16.

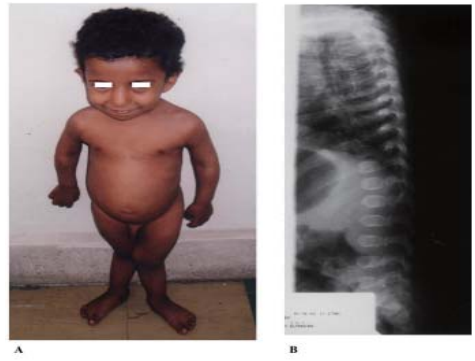

Fig. 9: Case 13 with SEMDJL at 3 years and 8 months of age. Frontal view showing clinical features and joint laxity of knees (A). X-ray (Lateral view) of thoracolumbar spine showing flat vertebrae with anterior beaking (B).

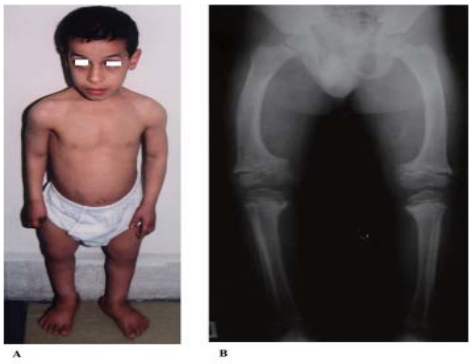

Fig. 10: Case 14 with SEMDJL at 8 years of age. Frontal view showing clinical features (A). X-ray of pelvis and long bones of lower limbs showing shallow acetabulum, oblique bowed femora, widening and fraying of metaphyses and indentations of epiphyses (B).

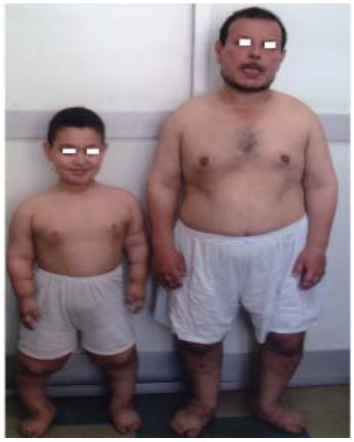

Fig. 11: Frontal view showing clinical features in case 15 with SEMDJL at 10 years of age and his similarly affected father.

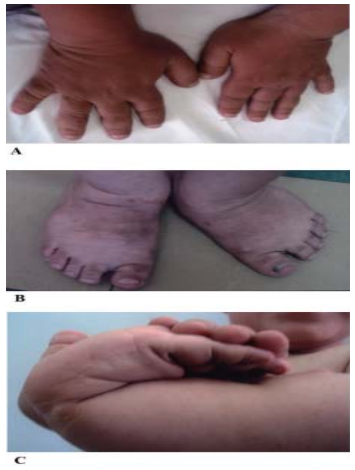

Fig. 12: Hands and feet of the father of case 15 with SEMDJL showing brachydactyly and spatulate distal phalanges (A & B). Left upper limb of case 15 with hyperextensibility of wrist and interphalangeal joints (C).

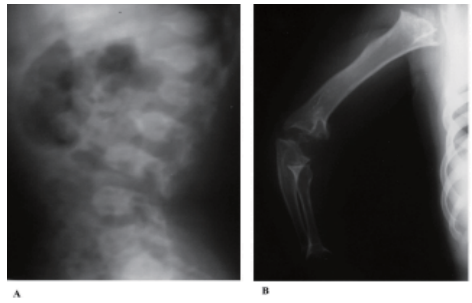

Fig. 13: X-ray (Lateral view) of lumbar vertebrae of the father of case 15 with flat rounded vertebrae with anterior beaking and increased lumbar lordosis (A). X-ray of right upper limb of case 15 showing short irregular long bones with irregular wide metaphyses and small epiphyses (B).

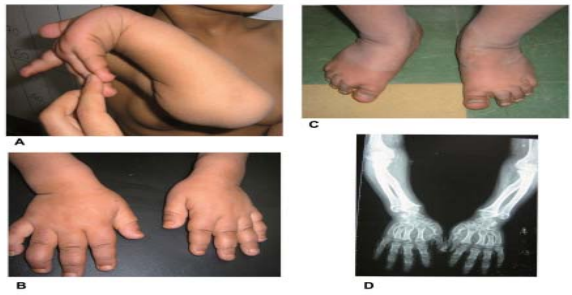

Fig. 14: Case 16 with SEMDJL at 14 years of age. Right upper limb showing hyperextensibility of wrist and interphalangeal joints (A). Hands with brachydactyly and spatulate ends of distal phalanges (B). Short broad feet with short toes and broad big toes (C). X-ray (PA view) of forearms and hands showing irregular long bones, radius overriding head of humerus, flaring of metaphyses and short metacarplas (D)

Table 2: Genetic, clinical & radiological data of subtype IV (cases 13-16).

Case no.	Sex	Age	Consanguinity	Family History	Facial & dental manifestations	Other clinical features	Radiological findings	Others
Case 13 **(Fig. 9A)**	M	3y 8m	+	Similarly affected sib	Triangular face, prominent eyes, prominent nose, long philtrum, microstomia, micrognathia, cleft uvula and palate, thick alveolar ridges, deep overbite and wide overjet.	Short neck, narrow chest, flaring of lower ribs, winged scapulae, hyperlordosis, bilateral clinodactyly of 5th fingers, knock knees, **hyperextensibility of knees, interphalangeal joints (IP) and wrists.**	Anterior clefting and beaking of vertebrae **(Fig. 9 B),** lumbar hyperlordosis, scoliosis, small epiphyses, metaphyseal widening.	IQ: 67
Case 14	M	8y	+	Similarly affected sib	Oval face, prominent eyes, midface hypoplasia, prominent nose, flat philtrum, thick lips, prominent premaxilla, high arched palate, malocclusion, micrognathia	Short sternum, pectus excavatum, lumbar lordosis, brachydactyly, right simian crease, **hyperextensibility of IP joints and wrists,** broad big toes, clinodactyly of little toes, prominent heels.	Mild obliterated lumbar lordosis and scoliosis, narrow pelvis, shallow acetabulum, oblique femur, bowing of femur, triangular end of upper humerus, widening and fraying of metaphyses and indentation of epiphyses **(Fig. 10 B).**	Hirschsprung disease at birth operated upon at 1.5 months of age.
Case 15 **(Fig. 11)**	M	10y	-	Similarly affected father **(Fig. 11, 12 A, B & 13 A)**	Prominent eyes, fissured lips, high arched palate.	Pectus carinatum, transverse crease in the forearm, **hyperextensibility of IP & wrist joints (Fig. 12 C),** brachydactyly with spatulate distal phalanges, bow legs, genu varum.	Flat rounded vertebrae with anterior tongue projections, decreased inter vertebral disc spaces, scoliosis, hypoplastic epiphyses, wide metaphyses, wide joint spaces, short broad metacarpals **(Fig. 13 B).**	Myopia
Case 16	F	14y	-	-	Micrognathia, high arched palate.	Flaring of ribs, Harissons sulcus, lunbar lordosis, bow legs, **hyperextensibility of IP and wrist joints,** brachydactyly with spatulate distal phalanges **(Fig. 14 A, B, C).**	Platyspondyly, scoliosis, lumbar lordosis, flaring of metaphyses, radius overriding head of humerus, short metacarpals **(Fig. 14 D)**	-

Sub-type V: Presented by 2 cases (Cases 17, 18)

Case (17) a female patient, offspring of first cousins parents. She was referred at 11 years and 3 months of age due to short stature, her height was below normal (-5.32 SD). She had 2 similarly affected male sibs, who were not available for examination. Her father was short with pectus deformity, hyperlordosis and myopia (Family pedigree figure 1g). She has normal mentality and no dysmorphic features. Orodental examination showed long philtrum, prominent premaxilla, prominent collumella, labial inclination of upper and lower anterior raphe and prominent median palatine taphe. Clinical examination revealed short neck, narrow short chest, pectus carinatum, bowing of lower limbs, brachydactyly and sandal gap between 1st and 2nd toes. Chest, heart and abdomen were clinically free. Overriding thin oblique ribs, platyspondyly with posterior wedging of vertebrae, irregular lower ends of femur, upper and lower tibia and lower fibulae, fragmented flattened epiphyses, mottling of metaphyses at the upper end of femur, proximal club shaped proximal femurs and shallow acetabular roof were evident by skeletal survey. Hearing assessment and eye evaluation were normal. Chest, heart and abdomen were clinically free.

Case (18) an 8 years old male patient, offspring of non-consanguineous parents, whose ages at his birth were 36 years (Father) and 31 years (Mother) with a history of a similarly affected aunt, his paternal grandparents are non-consanguineous and his father was not available for examination (Family pedigree figure 1h). His height at presentation was below normal (-3.8 SD) with increased U/L segment ratio while his head circumference was slightly above the mean for his age. He had normal mentality, prominent philtrum, small low set ears, macrognathia, short hyperextensible neck, short trunk with exaggerated lumbar lordosis, flaring of ribs, knock knees and broad short hands Figure (15). Orodental examination showed macroglossia, partial ankyloglossia, thick alveolar ridge, deep overbite and wide diastema. Chest, heart and abdomen were clinically free.

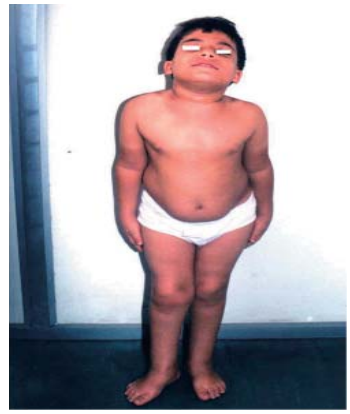

Fig. 15: Frontal view of case 18 with SEMD-Strudwick type at 8 years of age showing clinical features.

Skeletal survey revealed dysplastic acetabulum, small square iliac blades, narrow sacrosciatic notch, bilateral shortening and broadening of femoral necks, fragmentation of greater and lesser trochanters, genu valgus,

metaphyseal widening and flattened vertebrae with increased intervertebral spaces (Figure 16a, b).

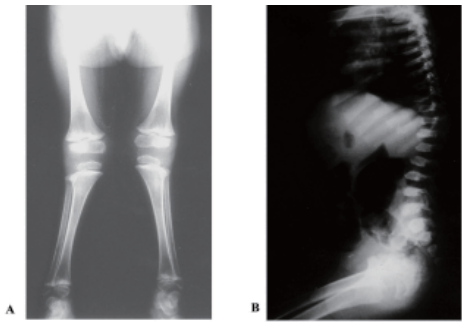

Fig. 16: Radiological findings in case 18. X-ray of long bones of lower limbs showing genu valgus and broad metaphyses (A). Lateral view of thoracolumbar vertebrae and pelvis showing platyspondyly with increased joint spaces, shortening and broadening of femoral neck and fragmentation of greater and lesser trochanters (B).

Hearing assessment and eye evaluation were normal. Chest, heart and abdomen were clinically free. Pelvic ultrasound revealed irregular dense calcification of the middle region of the right kidney, which might be attributed to the long duration of calcium and vitamin D supplementation. Renal function tests and calcium and vitamin D levels in blood were normal.

Sub-type VI: SEMD with hypotrichosis.

Case (19) presented at the age of 2 years and 2 months. She is the offspring of consanguineous normal parents with no family history of any affected members. The father was 35 years and the mother was 29 years at her birth. Her height at examination was below normal (-5.1 SD) with increased U/L segment ratio. She was not able to stand unsupported at that age. She had a dolicocephalic skull with bitemporal recession, sparse scalp hair, long flat face, prominent forehead, downward slanting of palpebral fissures, broad nasal root, short nose, long philtrum, microstomia and thin upper lip. Clinical examination revealed short neck, short limbs and short broad hands with tapered fingers Figure (17a, b, c). Chest, heart and abdomen were clinically free apart from a small birth mark at the right hypochondrium. Orodental examination showed relative macroglossia, high arched palate and narrow vault with crowding of teeth.

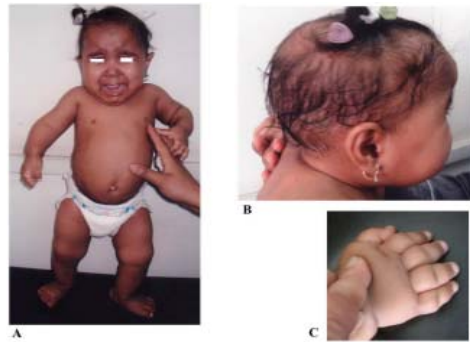

Fig. 17: Case 19 with SEMD with hypotrichosis at 2 years and 2 months of age. Frontal view showing clinical features (A). Lateral view of head showing hypotrichosis and midface hypoplasia (B). Right hand with brachydactyly and tapered fingers (C).

Skeletal survey showed platyspondyly with anterior beaking Figure (18a) and broad irregular metaphyses Figure (18b) in addition to brachydactyly and hypoplastic terminal phalanges.

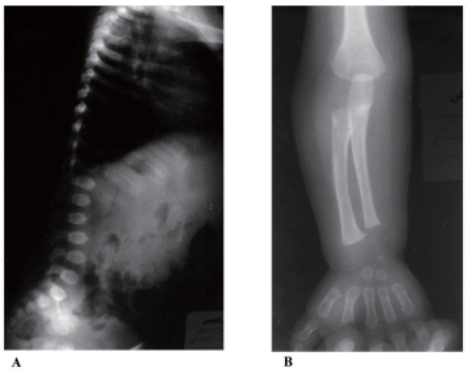

Fig. 18: Radiological findings in case 19. Lateral view of thoraco-lumbar vertebrae showing platyspondyly with anterior beaking (A). Left forearm showing broad irregular metaphyses and short metacarpals (B).

Sub-type VII: Case (20) a 1 year and 2 months old female, the only child of non-consanguineous young parents. She was able to stand unsupported. Facial features included long face, high forehead, narrow palpebral fissures, malar hypoplasia, depressed nasal bridge, microstomia, thick lips and retrognathia. Orodental examination showed high arched palate, thick labial frenum, prominent median palatine raphe and thick alveolar ridge. Clinical examination revealed short neck, short rhizomelic bowed limbs, mild kyphosis, flaring of lower ribs, pectus carinatum, limited extension of knees and elbows, fusiform fingers with camptodactyly and overriding 2nd toes bilaterally. Figure (19) shows her clinical features.

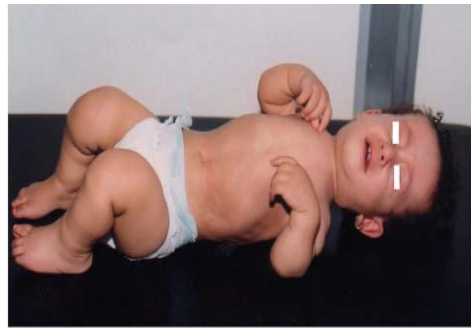

Fig. 19: Whole body of case 20 at 1 year and 2 months of age showing clinical features.

Main radiological features included narrow chest with short ribs, platyspondyly with increased intervertebral spaces, short long bones with defective epiphyseal mineralization and cupping of metaphyses in addition to flat acetabular roof.

Estimation of GAGs in urine and enzyme activity assays of MPS was normal for cases 11- 20.

DISCUSSION

SEMDs are a heterogeneous group of chondrodysplasias with different patterns of inheritance. Patients are characterized by short stature which is disproportionate in most cases. SEMDs are distinguished from the SEDs and SMDs by the combined involvement of the epiphyses and metaphyses in addition to malformations of the

vertebrae which are common in the three types. Different subtypes were reported in genetic medical databases and literature. In this study cases were classified based on additional characteristic clinical or radiological features into 7 subtypes and will be discussed separately.

Sub-type I: Dyggve-Melchior-Clausen disease (DMC) (OMIM: 223800):

Our study included 5 unrelated families with 9 affected patients (Cases 1-9) consistent with the clinical and radiological findings of DMC syndrome. All were the offspring of healthy consanguineous parents, the first 4 cases were affected sibs from one family and cases 5, 6 were affected sibs from the second family indicating an autosomal recessive pattern of inheritance. Their heights were below normal (-3.7 to -7.5 SD) with decreased U/L segment ratio. Mental retardation, microcephaly and characteristic radiological manifestations including the characteristic lace like appearance of iliac crests were consistent findings in all cases. Prominent jaw was a common finding and was described in DMC syndrome by Beighton.[7]

DMC is an autosomal recessive disorder, first described by Dyggve et al.[8] in 3 children, offspring of consanguineous parents. The syndrome is characterized by mental retardation and microcephaly. Radiological features in addition to epiphyseal dysplasia and irregular metaphyses include platyspondyly with central constriction of vertebral bodies that becomes more evident in late childhood.[9] In adults the vertebral bodies become more rectangular.[10] A pathognomonic radiological sign is small iliac wings with lacy appearance of iliac crests, which was found to be caused by bone tissue deposited in a wavy pattern at the osteochond-ral junction.[11]

Other frequently noted dysmorphic facial and orodental features in our patients included narrow forehead, long philtrum, macrostomia with thick lips, high arched palate, malocclusion, macrodontia and lobulated tongue. Hirsutism, limited extension of elbow joints, dysplastic nails, camptodactyly of distal phalanges, bilateral pes cavus and short low inserted big toes were noted in some of our described cases. Cases 1, 2 had central and cortical brain atrophy evident by CT scan while case (2) had dysarthric speech and stereotyped movements. These additional manifestations expand the phenotypic spectrum of DMC syndrome. Characteristic facial dysmorphism and body habitus suggest the diagnosis which is confirmed by radiological findings.

Differential diagnosis includes MPS (Types I, IV). The absence of corneal clouding, deafness and cardiac anomalies in addition to the characteristic radiological findings of DMC differentiates both conditions clinically although enzyme assays is essential for definite diagnosis. Biochemical analysis of our studied cases showed an increased amount of GAGs in urine while enzyme assays excluded the presence of mucopolysacharridosis. Engfeldt et al.[12] found increased amounts of GAGs in the cartilage in cases with DMC and indicated that the ability of proteoglycan monomers to reaggregate to hyaluronic acid chains was decreased

thus supporting the suggestion that DMC dysplasia is due to disturbance in proteoglycan metabolism. Electron microscopic studies of DMC chondrocytes and fibroblasts by the same authors[12] revealed enlarged endoplasmic reticulum vessels suggesting the possibility of a storage disease.

Linkage studies using homozygosity mapping have led to the localization of the disease causing gene (DYM), on chromosome 18q12- q21.1.[13,14] Sixteen different mutations have been described by Paupe et al.[15]. The fact that many reported cases came from an Arab origin; cases from Moracco, Gaza[10], Lebanon[16,17,18] and Egypt[19] in addition to 9 affected cases in 5 families in this report suggests a relatively high frequency of the DYM gene in Arabs, which is a finding that needs further confirmation. DYM mutations with at least five founder effects in Morocco, Lebanon and Guam Island were reported by Paupe et al.[15]. It would be of interest to characterize the mutations of our cases.

Sub-type II: Smith-McCort Dysplasia (SMC) (OMIM: 607326):

Case (10) in this study was consistent with SMC dysplasia. Being the offspring of first cousins parents is in consistence with the autosomal recessive nature of the disease. Short limbs and trunk with barrel shaped chest and normal mentality in addition to the characteristic lace like appearance of iliac crests, diagnostic of SMC dysplasia, were evident in our patient. Orodental findings in our case included everted lower lip, macroglossia, enamel hypoplasia and hypocalcification, amelogenesis imperfecta and prognathism. The decreased bone density seen by X-ray was confirmed by DEXA that showed border line osteoporosis at the pelvis. SMC is a rare autosomal recessive variant of DMC syndrome without mental retardation or microcephaly. It was shown to be allelic to DMC syndrome and results from mutations in DYM gene that would be less deleterious to the brain.[15,20]

Nakamura et al.[11] concluded that SMC syndrome has pathologic changes in common with DMC disease as endoplasmic reticulum storage disorder even though the mental condition is different.

The differential diagnosis includes MPS type IV which was excluded in our case by the normal enzyme activity of Morquio disease, although GAGs in urine were high for age as in cases with DMC dysplasia.

Sub-type III: SEMD, X-linked with mental deterioration (OMIM: 300232):

Cases (11, 12) in this study were affected male sibs with 2 similarly affected brothers and a normal female sib, who were not available for examination. The fact that all affected sibs were males with no male to male transmission and the presence of microcephaly, mental retardation, the progressive nature of the disorder and the absence of the lacy appearance of iliac crests characteristic of DMC syndrome makes SEMD, X-linked with mental retardation the most likely diagnosis.

This distinct form of SEMD was described only once by Bieganski et al.[21] in 3 boys in a pattern consistent

with X-linked recessive inheritance. The syndrome is characterized by its progressive nature. Case (11) in this study was bedridden at 18 years of age with dysarthric speech and joint contractures similar to one of the cases described by Bieganski et al.[21]. Previously described cases had abnormal CT/MRI findings in the form of small corpus callosum, cortical atrophy and markedly delayed myelination. Cortical atrophy and hypogenesis of corpus callosum were evident by CT scan brain in case (11).

The disorder is distinguished from X-linked SEMD (OMIM: 300106) described by Camera et al.[22] based on the presence of microcephaly and mental retardation, which were not described in X-linked SEMD. Dysarthric speech, limited extension of elbows and cortical brain atrophy present in cases 11, 12 were noted in some of our described cases with DMC syndrome (Cases 1-9), although an X-linked form of DMC syndrome with normal intelligence was described by Yunis et al.[23] (OMIM: 304950), the presence of mental retardation, the progressive nature of the disease and the absence of the characteristic lacy appearance of iliac crests in our cases distinguishes this type from DMC syndrome.

Another type of SEMD with mental retardation, microcephaly, ataxia and dysmorphic features without lacy iliac pelvic crest and absence of mutation in the DYM gene was described by Genevieve et al.[24]. The autosomal recessive pattern of inheritance and the presence of ataxia in the SEMD Genevieve type (OMIM 610442) differentiate it from the X-linked SEMD MR form. Molecular studies are needed to distinguish between these disorders and exclude the possibility of allelic variations.

Sub-type IV: SEMD joint laxity (OMIM: 271640):

Four of our patients (Cases 13-16) were consistent with this type of SEMD. Our cases were short with increased U/L segment ratio. Hyperextensibility was more marked in the wrists and interphalangeal joints with limited movement at the elbows of cases 15, 16a distinctive type of SEMD associated with **joint laxity** and scoliosis (SEMDJL) was described by Beighton et al.[25]. Joint laxity was especially striking in the hands with foreshortened fingernails and spatulate terminal phalanges. Hyperextensibility and instability of most joints with limited extension and supination of the elbows were reported by Bradburn and Hall.[26] Oval face with prominent eyes, flat midface, long flat philtrum and micrognathia were noted in our patients. These features were described by Beighton et al.[27] and Bradbum and Hall.[26] Cleft palate was present in several described cases, all our cases had high arched palate, case 13 had a similarly affected sister with cleft palate who died early in infancy from CHD. Radiological findings in our patients were consistent with those described by Bradbum and Hall[26] including scoliosis, rounded platyspondyly with anterior tongue projections of vertebrae in addition to flat dysplastic acetabulum, bat like appearance of iliac bones, coxa valga, hypoplastic epiphyses, widening and fraying of metaphyses and generalized brachydactyly of hands and feet with

particularly short metacarpals and distal enlargement of metaphyses. The authors stated that many of the typical findings evolve over time.

Vertebral abnormalities and ligamentous laxity result in spinal malalignment, progressive severe scoliosis and thoracic asymmetry that may result in death from respiratory compromise in the first or second decade in addition to the development of spinal cord compression and paraplegia.[28] Case (13) had asymmetry of chest with over crowded ribs, while case (14) had short sternum, pectus excavatum and scoliosis. Case (16) had flaring of ribs, back pain with progressive scoliosis. Although, Beighton[28] stated that no affected person over the age of 25 years had been reported, Tsirikos et al.[29] described a 35 years old female patient with SEMDJL with a favorable outcome. The father of our case 15 was seen by us at age 43 years and has all manifestations consistent with SEMDJL without developing the severe complications.

Other reported manifestations included CHD, mental retardation, megaureter, Hirschprung disease, myopia and dislocated lens.[2] Cases (13, 14) in this study had similarly affected sibs who died during early infancy from CHD, a common cause of death in some described cases. Case (13) had mild mental retardation (IQ: 67), case (14) had Hirschsprung disease that was operated upon after birth, while case (15) and his father had myopia.

Although previously described cases by Beighton et al.[27] were not the offspring of related parents some were affected sibs, patients described by Farag et al.[30] were the offspring of consanguineous parents with affected sibs suggesting a probable autosomal recessive pattern of inheritance. Cases (13, 14) in this study were the offspring of consanguineous parents with similarly affected sibs supporting the autosomal recessive pattern of inheritance. Case (15) had a similarly affected father with no consanguinity of parents. Case (16) is the offspring of non-consanguineous parents who were old at her birth. Both cases 15, 16 in the present study and unrelated cases described by Smith et al.[31] suggest the presence of an autosomal dominant variant of the disorder.

In linkage studies Beighton et al.[28] obtained significant negative results with proposed candidate loci including COL1A1, COL1A2, COL2A1, fibrillin and elastin.

Sub-type V: SEMD-Strudwick type (OMIM: 184250):

Features of SEMD-Strudwick type include short stature, pectus carinatum and scoliosis, with normal mentality resembling Morquio disease. These features were present in our cases (17, 18). Cleft palate and retinal detachment were frequently reported yet not present in our cases. The eponym Strudwick is derived from a prototype Amish patient at Johns Hopkins Hospital.[32]

Delayed epiphyseal maturation is present at birth while distinctive mottling of metaphyses (Dappling) a distinctive radiological feature resulting from alternating zones of osteosclerosis and osteopenia; develops with age.[33] This was clearly seen in our patients.

Anderson et al.[33] observed affected sibs with normal parents and favored autosomal recessive inheritance. In the present study cases (17, 18) were offspring of unrelated parents. Case (17) had an affected father and 2 affected brothers while case (18) had an affected aunt. Our cases support the autosomal dominant pattern of inheritance which was also supported by Tiller et al.[34,35], who demonstrated heterozygosity for a mutation in the COL2A1 gene establishing dominant inheritance. Sulko et al.[36] described monozygotic twin girls who showed heterozygosity for a missense mutation of the COL2A1 gene by sequencing.

Sub-type VI: SEMD with hypotrichosis (OMIM: 183849):

One of the included patients in the present study (Case 19) had congenital hypotrichosis, mild rhizomelic short stature and genu varum. Radiological features included mild metaphyseal flaring, irregular epiphyses and pear shaped vertebrae. Features are consistent with SEMD with hypotrichosis described by Whyte et al.[37,38] and Leonard and Hughes.[39] The authors stated that rhizomelia affects the upper limbs more than the lower limbs and the changes in the long bones were greatest in the proximal limbs as shown in our patient. No changes were reported in the teeth or nails. Orodental evaluation in our studied case showed macroglossia, high arched palate, narrow vault and crowding of teeth with no manifestations of hypodontia or peg shaped teeth and nails were normal.

Whyte et al.[37,38] described 5 affected members in 3 successive generations with the grandmother apparently representing a new mutation. Our case is sporadic; the offspring of consanguineous appa-rently healthy parents whose ages at her birth were 35 and 28 years old.

Sub-type VII:

Case (20) in the present study has clinical and radiological features that resemble SEMD-Irapa type (OMIM: 271650), first described by Arias et al.[40]. Clinical manifestations in our case included normal mentality, short stature with height below normal (-4.68 SD), joint pain and enlargement with limited extension of both elbows and knees, wide costochondral junctions, flaring of lower ribs, pectus carinatum, kyphosis, bowing of tibia and fibula and brachydactyly. Radiological examination revealed platyspondyly with increased intervertebral disc spaces, short bowed long bones with defective epiphyseal mineralization, cupping of metaphyses, flat acetabuler roof, coxa vara and short ribs with narrow chest. Both Arias et al.[40] and Hernandez et al.[41] described a form of SEMD among the Irapa Indians of Venezuela and 3 sibs from a Mexican mestizo family. Features included short spine due to platyspondyly, short metacarpals and metatarsals, and striking changes in the proximal femoral and distal humeral epiphyses. Arias[42] suggested SEMDI as a simple designation.

Receding anterior hair line, long face, narrow palpebral fissures, malar hypoplasia, retrognathia, low set ears and short neck were additional features in our case (20).

Another differential diagnosis included SEMD-Pakistani type (OMIM: 603005). The disorder was described by Ahmad et al.[43] and ul Haque et al.[44]. It is characterized by short bowed lower limbs, enlarged knee joints, joint stiffness, kyphoscoliosis, mild brachydactyly, early onset degenerative joint disease and limited movement of fingers. Radiological findings included delayed epiphyseal ossification at the hips and knees with mild metaphyseal involvement and platyspondyly. Both conditions were described in offspring of consanguineous parents, yet our patient was sporadic, offspring of non consanguineous parents. Both disorders had overlapping manifestations with joint stiffness and contractures. In SEMD-Pakistani type, PAPS synthetase referred to as SK1 or ATPSK2 was mapped to 10q23-q24.[45] Kurima et al.[46] isolated SK2; an additional member of the PAPS synthetase family. Xu et al.[47,48] mapped the PAPSS2 gene to 10 q22- q23 and sought common genetic polymorphisms in PAPSS2 that do not completely inactivate the enzyme and might lead to individual differences in sulfate conjugation. Further molecular studies of reported cases, in addition to our patient are essential for accurate definition of the disorder.

In summary, SEMD are genetically heterogeneous. Although all cases share generalized changes in vertebrae, epiphyses and metaphyses of long bones, additional associated clinical manifestations and pathognomonic radiological features were reported in different types and different molecular defects were identified in some cases and not yet identifiable in others. For classification purposes, pathogenetic and molecular criteria are integrating with morphological ones. With the great advances in molecular techniques it is necessary to identify the molecular bases for different types of SEMD for proper genetic counseling and prenatal diagnosis. Molecular diagnosis leads to confirmation of individual entities, characterization of new subtypes and might provide evidence of the great heterogeneity of these disorders.

REFERENCES

1. National Center for biotechnology Information. Online Mendelian Inheritance in Man. Available at: http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim.

2. Winter RM and Baraitser M. .The London Medical Database.2006Oxford University Press, Oxford.

3. Superti Furga A, Unger S. Nosology and classification of genetic skeletal disorders: 2006 revision. Am. J. Med. Genet. A. 2007 Jan 1; 143 (1): 1-18.

4. Whitley CB, Draper KA, Dutton CM, Brown PA, Severson SL, France LA. Diagnostic test for mucopolysaccharidosis. II. Rapid quantification of glycosaminoglycan in urine samples collected on a paper matrix. Clin.Chem. 1989 Oct; 35 (10): 2074-81.

5. Meikle PJ, Ranieri E, Ravenscroft EM, Hua CT, Brooks DA, Hopwood JJ. Newborn screening for lysosomal storage disorders. Southeast Asian J.Trop. Med. Public Health 1999; 30 Suppl 2: 104-10.

6. Kresse H, von Figura K, Klein U, Glossl J, Paschke E, Pohlmann R. Enzymic diagnosis of the genetic mucopolysaccharide storage disorders. Methods Enzymol. 1982; 83: 559-72.

7. Beighton P. Dyggve-Melchior-Clausen syndrome. J. Med. Genet. 1990 Aug; 27 (8): 512-5.

8. Dyggve HV, Melchior JC, Clausen J. Morquio-Ulrich's disease: An inborn error of metabolism? Arch. Dis. Child. 1962; 37: 525-34.

9. Spranger J, Maroteaux P, Der Kaloustian VM. The Dyggve-Melchior-Clausen syndrome. Radiology 1975 Feb; 114(2): 415-21.

10. Schorr S, Legum C, Ochshorn M, Hirsch M, Moses S, Lasch EE, et al. The Dyggve-Melchio-Clausen syndrome. AJR Am. J. Roentgenol. 1977 Jan; 128 (1): 107-13.

11. Nakamura K, Kurokawa T, Nagano A, Nakamura S, Taniguchi K, Hamazaki M. Dyggve-Melchior-Clausen syndrome without mental retardation (Smith-McCort dysplasia): Morphological findings in the growth plate of the iliac crest. Am. J. Med. Genet. 1997 Oct 3; 72 (1): 11-7.

12. Engfeldt B, Bui TH, Eklof O, Hjerpe A, Reinholt FP, Ritzen EM, et al. Dyggve-Melchior-Clausen dysplasia. Morphological and biochemical findings in cartilage growth zones. Acta Paediatr.Scand. 1983 Mar; 72 (2): 269-74.

13. Thauvin Robinet C, El Ghouzzi V, Chemaitilly W, Dagoneau N, Boute O, Viot G, et al. Homozygosity mapping of a Dyggve-Melchior-Clausen syndrome gene to chromosome 18q21.1. J. Med. Genet. 2002 Oct; 39 (10): 714-7.

14. Cohn DH, Ehtesham N, Krakow D, Unger S, Shanske A, Reinker K, et al. Mental retardation and abnormal skeletal development (Dyggve-Melchior -Clausen dysplasia) due to mutations in a novel, evolutionarily conserved gene. Am. J. Hum. Genet. 2003 Feb; 72 (2): 419-28.

15. Paupe V, Gilbert T, Le Merrer M, Munnich A, Cormier Daire V, El Ghouzzi V. Recent advances in Dyggve-Melchior-Clausen syndrome. Mol. Genet. Metab. 2004 Sep-Oct; 83 (1-2): 51-9.

16. Naffah J. The Dyggve-Melchior-Clausen syndrome. Am. J. Hum. Genet. 1976 Nov; 28 (6): 607-14.

17. Bonafede RP, Beighton P. The Dyggve-Melchior-Clausen syndrome in adult siblings. Clin. Genet. 1978 Jul; 14 (1): 24-30.

18. Neumann LM, El Ghouzzi V, Paupe V, Weber HP, Fastnacht E, Leenen A, et al. Dyggve-Melchior-Clausen syndrome and Smith-McCort dysplasia: Clinical and molecular findings in three families supporting genetic heterogeneity in Smith -McCort dysplasia. Am. J. Med. Genet. A. 2006 Mar 1; 140 (5): 421-6.

19. El Sayed SM. Dyggve-Melchior-Clausen syndrome: Case report. Egypt. J. Med. Hum. Genet. 2005; 6: 67-72.

20. Ehtesham N, Cantor RM, King LM, Reinker K, Powell BR, Shanske A, et al. Evidence that Smith-McCort dysplasia and Dyggve-Melchior-Clausen dysplasia are allelic disorders that result from mutations in a gene on chromosome 18q12. Am. J. Hum. Genet. 2002 Oct; 71 (4): 947-51.

21. Bieganski T, Dawydzik B, Kozlowski K. Spondylo-epimetaphyseal dysplasia: A new X-linked variant with mental retardation. Eur. J. Pediatr. 1999 Oct; 158 (10): 809-14.

22. Camera G, Stella G, Camera A. New X linked spondyloepimetaphyseal dysplasia: Report on eight affected males in the same family. J. Med. Genet. 1994 May; 31 (5): 371-6.

23. Yunis E, Fontalvo J, Quintero L. X-linked Dyggve-Melchior-Clausen syndrome. Clin. Genet. 1980 Oct; 18 (4): 284-90.

24. Genevieve D, Heron D, El Ghouzzi V, Prost Squarcioni C, Le Merrer M, Jacquette A, et al. Exclusion of the dymeclin and PAPSS2 genes in a novel form of spondyloepimetaphyseal dysplasia and mental retardation. Eur. J. Hum. Genet. 2005 May; 13 (5): 541-6.

25. Beighton P, Kozlowski K, Gericke G, Wallis G, Grobler L. Spondylo-epimetaphyseal dysplasia with joint laxity and severe, progressive kyphoscoliosis. A potentially lethal dwarfing disorder. S. Afr. Med. J. 1983 Nov 5; 64 (20): 772-5.

26. Bradburn JM, Hall BD. Spondyloepimetaphyseal dysplasia with joint laxity (SEMDJL): Clinical and radiological findings in a Guatemalan patient. Am. J. Med. Genet. 1995 Nov 6; 59 (2): 234-7.

27. Beighton P, Gericke G, Kozlowski K, Grobler L. The manifestations and natural history of spondylo-epi-metaphyseal dysplasia with joint laxity. Clin. Genet. 1984 Oct; 26 (4): 308-17.

28. Beighton P. Spondyloepimetaphyseal dysplasia with joint laxity (SEMDJL). J. Med. Genet. 1994 Feb; 31 (2): 136-40.

29. Tsirikos AI, Mason DE, Scott CI,Jr, Chang WN. Spondyloepimetaphyseal dysplasia with joint laxity (SEMDJL). Am. J. Med. Genet. A. 2003 Jun 15; 119 (3): 386-90.

30. Farag TI, Al Awadi SA, Hunt MC, Satyanath S, Zahran M, Usha R, et al. A family with spondyloepimetaphyseal dwarfism: A "new" dysplasia or Kniest disease with autosomal recessive inheritance? J. Med. Genet. 1987 Oct; 24 (10): 597-601.

31. Smith W, Ji HP, Mouradian W, Pagon RA. Spondyloepimetaphyseal dysplasia with joint laxity (SEMDJL): Presentation in two unrelated patients in the United States. Am. J. Med. Genet. 1999 Sep 17; 86 (3): 245-52.

32. Murdoch JL, Walker BA. A ''new'' form of spondylometaphyseal dysplasia. Birth Defects Orig. Art. Ser. 1969; 5 (4): 368-70.

33. Anderson CE, Sillence DO, Lachman RS, Toomey K, Bull M, Dorst J, et al. Spondylometepiphyseal dysplasia, Strudwick type. Am. J. Med. Genet. 1982 Nov; 13 (3): 243-56.

34. Tiller GE, Weis MA, Lachman RS, Cohn DH, Rimoin DL, Eyre DR. A dominant mutation in the type II collagen gene (COL2A1) produces spondyloepimetaphyseal dysplasia (SEMD) Strudwick type, abstract. Am. J. Med. Genet. 1993; 53: A209.

35. Tiller GE, Polumbo PA, Weis MA, Bogaert R, Lachman RS, Cohn DH, et al. Dominant mutations in the type II collagen gene, COL2A1, produce spondyloepimetaphyseal dysplasia, Strudwick type. Nat. Genet. 1995 Sep; 11 (1): 87-9.

36. Sulko J, Czarny Ratajczak M, Wozniak A, Latos Bielenska A, Kozlowski K. Novel amino acid substitution in the Y-position of collagen type II causes spondyloepimetaphyseal dysplasia congenita. Am. J. Med. Genet. A. 2005 Sep 1; 137 (3): 292-7.

37. Whyte MP, Petersen DJ, McAlister WH. Hypotrichosis with spondyloepimetaphyseal dysplasia in three generations: A "new" autosomal dominant syndrome. Am. J. Med. Genet. 1990; 36 (3): 288-91.

38. Whyte MP, Petersen DJ, McAlister WH. Hypotrichosis with spondyloepimetaphyseal dysplasia in three generations: A "new" autosomal dominant syndrome. Am. J. Med. Genet. 1990 Jul; 36 (3): 288-91.

39. Leonard NJ, Hughes HE. An unknown spondyloepimetaphyseal dysplasia with a positive sweat chloride test, sparse hair and mild facial dysmorphism. Clin. Dysmorphol. 1994 Oct; 3 (4): 309-17.

40. Arias S, Mota M, Pinto Cisternas. L'osteochondrodysplasie spondylo-epiphyso-metaphysaire type Irapa. Nouveau nanisme avec rachis et metatarsiens courts [Irapa type spondylo-epiphyso -metaphyseal osteochondrodysplasia. New type of dwarfism with short spine and metatarsals]. Nouv.Presse Med. 1976 Feb 7;5 (6): 319-23.

41. Hernandez A, Ramirez ML, Nazara Z, Ocampo R, Ibarra B, Cantu JM. Autosomal recessive spondylo-epi-metaphyseal dysplasia (Irapa type) in a Mexican family: Delineation of the syndrome. Am. J. Med. Genet. 1980; 5 (2): 179-88.

42. Arias S. Osteochondrodysplasia Irapa type: An ethnic marker gene in two subcontinents. Am. J. Med. Genet. 1981; 8 (2): 251-6.

43. Ahmad M, Haque MF, Ahmad W, Abbas H, Haque S, Krakow D, et al. Distinct, autosomal recessive form of spondyloepimetaphyseal dysplasia segregating in an inbred Pakistani kindred. Am. J. Med. Genet. 1998 Aug 6; 78 (5): 468-73.

44. Haque MF, King LM, Krakow D, Cantor RM, Rusiniak ME, Swank RT, et al. Mutations in orthologous genes in human spondyloepimetaphyseal dysplasia and the brachymorphic mouse. Nat. Genet. 1998 Oct; 20 (2): 157-62.

45. Li H, Deyrup A, Mensch JR,Jr, Domowicz M, Konstantinidis AK, Schwartz NB. The isolation and characterization of cDNA encoding the mouse bifunctional ATP sulfurylase- adenosine 5̀-phosphosulfate kinase. J. Biol. Chem. 1995 Dec 8; 270 (49): 29453-9.

46. Kurima K, Warman ML, Krishnan S, Domowicz M, Krueger RC,Jr, Deyrup A, et al. A member of a family of sulfate-activating enzymes causes murine brachymorphism. Proc. Natl. Acad. Sci.U.S.A. 1998 Jul 21;95 (15): 8681-5.

47. Xu ZH, Otterness DM, Freimuth RR, Carlini EJ, Wood TC, Mitchell S, et al. Human 3̀-phosphoadenosine 5̀-phosphosulfate synthetase 1 (PAPSS1) and PAPSS2: Gene cloning, characterization and chromosomal localization. Biochem. Biophys. Res. Commun. 2000 Feb 16; 268 (2): 437-44.

48. Xu ZH, Freimuth RR, Eckloff B, Wieben E, Weinshilboum RM. Human 3̀-phosphoadenosine 5̀-phosphosulfate synthetase 2 (PAPSS2) pharmacogenetics: Gene resequencing, genetic polymorphisms and functional characterization of variant allozymes. Pharmacogenetics 2002 Jan; 12 (1): 11-21.