

# Yunis-Varon syndrome with severe osteodysplasty

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## Abstract

**We report two male sibs and two female sibs from separate families, both with normal parents, who had a lethal condition with features of the Yunis-Varon syndrome and radiological signs of severe osteodysplasty. Autosomal recessive inheritance is likely in both families. The additional features described represent further delineation of the phenotype of the Yunis-Varon syndrome.**

The Yunis-Varon syndrome was recently reviewed by Hennekam and Vermeulen-Meiners<sup>1</sup> who added a further case to the seven reported previously. The condition was first described in 1980 when Yunis and Varon<sup>2</sup> reported five patients from three Columbian families with cleidocranial dysostosis, severe micrognathia, bilateral absence of the thumbs and first metatarsal bones, and distal aphyalangia. They all died before 10 weeks of age. The presence of consanguinity in three of the families reported and the lack of sex predilection were thought to be consistent with autosomal recessive inheritance.

The four patients whom we describe had similar hands and feet and similar facial features to those described in the Yunis-Varon syndrome. However, our cases did not have absent clavicles and one pair of sibs reported here had pathological fractures. All four had generalised skeletal changes, including supra-acetabular constrictions and flared metaphyses, not

previously described in the Yunis-Varon syndrome. These changes were similar to those described by Kozłowski *et al*<sup>3</sup> as a precocious type of osteodysplasia. They reported three babies, two of them sibs, who died in infancy. The radiological features resembled the osteodysplasty seen in the Melnick-Needles syndrome<sup>4,5</sup> and they suggested that there is a more severe form of this condition, probably inherited as an autosomal recessive trait.

The patients described below show features of both the Yunis-Varon syndrome and precocious osteodysplasty.

## Case reports

### CASE 1

Case 1, a male, was born to healthy, non-consanguineous parents who had one older healthy son. The mother was 35 and the father 29 at the time of the baby's birth. The pregnancy was uneventful and a routine ultrasound scan at 19 weeks' gestation was unremarkable. Labour occurred spontaneously at 39

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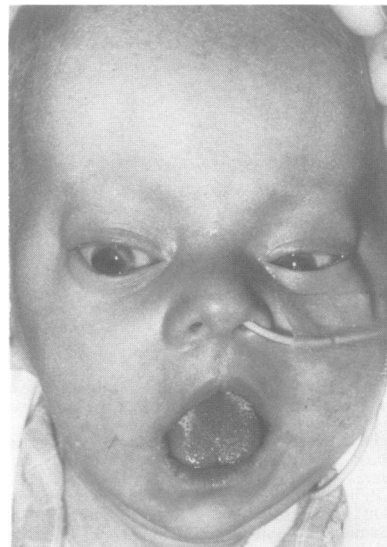
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*Figure 1 Case 1 (brother of case 2) aged 3 weeks. Note the sclerocornea, prominent eyes, bitemporal indentation, and small chin.*

weeks' gestation and the baby was born by normal vertex delivery, weighing 3030 g (>10th centile), length 52 cm (>50th centile). The head circumference was 33 cm (>2nd centile) and there was a large anterior fontanelle and small posterior fontanelle. The face was dysmorphic (fig 1) with prominent eyes and indentation of the temples. The corneal membrane over the outer part of the iris was opaque. The ears were low set with absent lobes, the nose was small, and the palate high arched. The chest was long and the liver and spleen were palpable. The kidneys were easily palpable but were normal on ultrasound examination. The testes were descended but the scrotum was bifid and there was coronal hypospadias. The hands and feet were particularly abnormal. The left thumb was absent, the right vestigial, and the fingers were short with very small nails (fig 2). The big toes were absent and the remaining toes short with poorly formed nails. The hips did not abduct fully. TORCH screen was negative and there was a normal male chromosome complement, 46,XY. CT scan showed a small mass thought to be a haematoma in the right parietal region.

The radiographs (figs 3 to 6) showed the following features. The iliac wings were flared and there were constrictions in the supra-acetabular regions, producing notching of the lateral borders. The acetabula were short and sloping and there was coxa valga with bilateral hip dislocation (fig 3). The scapulae were abnormal, with constrictions adjacent to the glenoid fossae. The metaphyses of the long bones were flared. The long bone diaphyses and ribs were slender, with irregular, thickened cortices. In the hands (fig 4) and feet (fig 5) the first metatarsals and metacarpals were absent, as were the phalanges of the thumbs and big toes. The distal phalanges of all the digits were absent, and the middle phalanges were absent or hypoplastic. There was an unusual coarse and stellate

trabecular pattern of ossification in the parietal and occipital bones (fig 6).

The baby had breathing difficulties initially and required oxygen for several days. At 3 months of age he was very floppy with no head control and did not

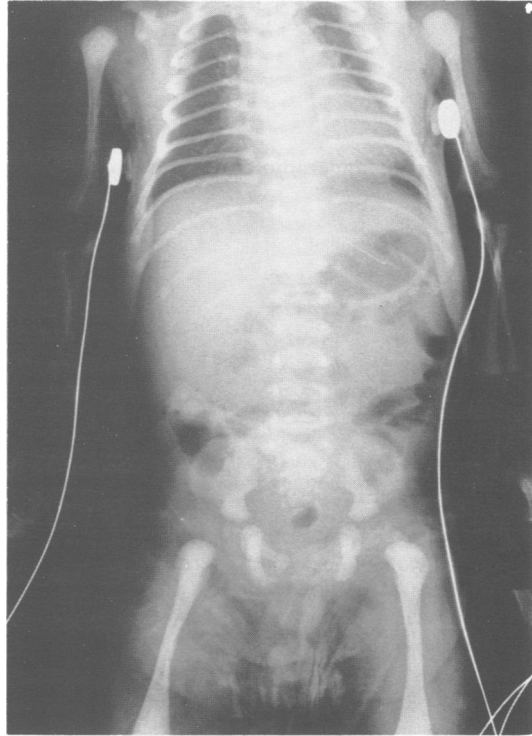


Figure 3 Case 1. Radiograph of trunk showing slender ribs and diaphyses of long bones, marked metaphyseal flaring, and flared iliac wings with supra-acetabular constrictions laterally.



Figure 2 Case 1. Left hand showing absence of thumb, short tapering fingers, and vestigial nails.



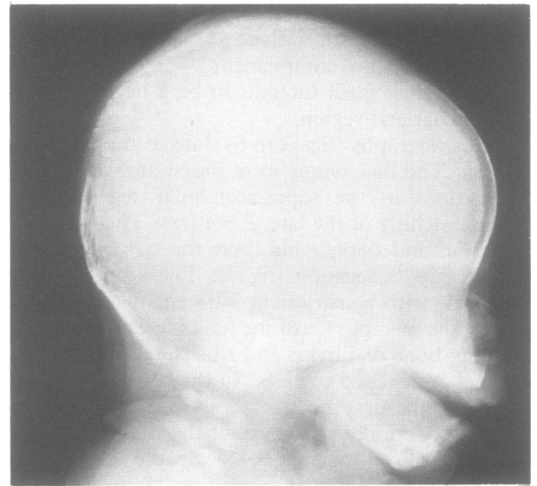
*Figure 4 Case 1. Radiograph of left hand showing absence of thumb and terminal phalanges, with short middle phalanges and metacarpals.*

fix or follow. His head circumference was 38.25 cm (2nd centile). He still required tube feeding and remained very weak, eventually dying of pneumonia at 4 months of age.

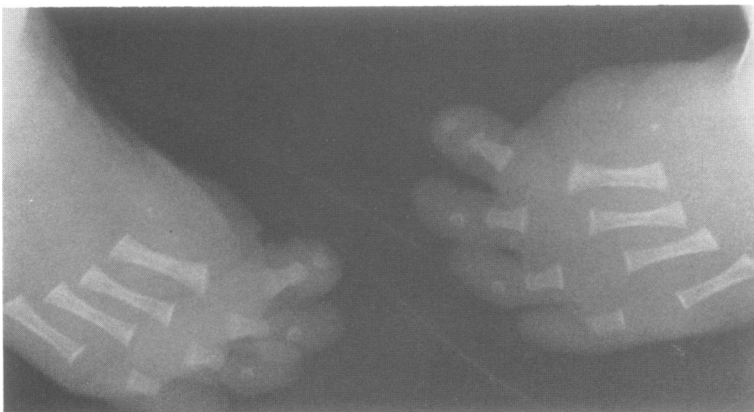
At necropsy his weight was 5.8 kg and length 55 cm, both well below the 3rd centile.

Internal examination confirmed the bronchopneumonia, but other abnormalities were limited to the central nervous system. The brain weighed 810 g and was generally swollen. Gross findings were absent olfactory bulbs and tracts, and a well circumscribed, approximately spherical mass 2.5 cm in diameter in

the posterior horn of the right lateral ventricle. This comprised a sparsely cellular mixture of glia, axons, and other elements attached to choroid plexus. Its exact nature was not clear, but it appeared to represent a type of hamartoma totally unlike, for example, the lesions of tuberous sclerosis. Elsewhere, there was neuronal loss and vacuolation involving the cerebral cortex (layers 3 and 5), the basal ganglia, cerebellar dentate nuclei, medullary olives, and spinal anterior horns. No abnormal storage material or ultrastructural inclusions were seen. The distribution was symmetrical and strongly suggested a hypoxic aetiology. Histochemical examination of the muscle showed moderate neurogenic atrophy, most probably secondary to the loss of spinal lower motor neurones. Thus, the neuropathological abnormalities were



*Figure 6 Case 1. The skull vault shows poor mineralisation, a coarse trabecular pattern, and an unusual stellate appearance in the parietal and occipital bones.*



*Figure 5 Case 1. Radiograph of feet, showing total absence of halluces and terminal phalanges with marked hypoplasia of middle phalanges.*

considered to fall into three groups: a major malformation (arhinencephaly), an unusual and possibly unrelated tumour, and changes resulting from hypoxia.

#### CASE 2

Shortly after the death of their son, the mother of case 1 became pregnant again, understanding that there was a significant risk of a second affected child. Ultrasound examination at 18 weeks could not show more than four digits on the limbs, so fetoscopy was performed by Mr Charles Rodeck and absence of the thumbs and big toes was confirmed.

Termination of pregnancy was performed by prostaglandin induction. The fetal weight was 250 g, placenta 140 g, length 24 cm, and head circumference 18 cm. The appearance was similar to the previous child, with a small chin and poorly formed ear lobes (fig 7). The thumbs and big toes were represented by stubs (fig 8) and the index fingers were poorly formed. Internally, the only abnormal finding was agenesis of the corpus callosum with associated dilatation of the occipital horns of the lateral ventricles.

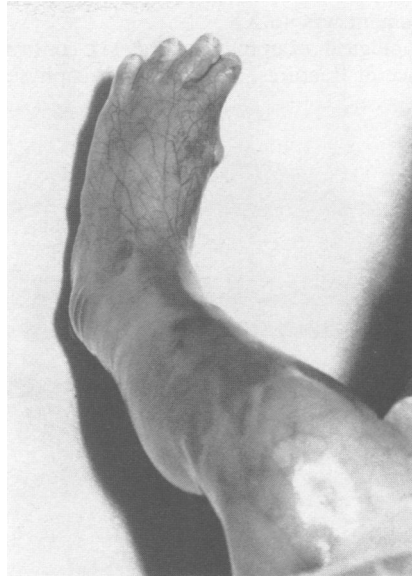


Figure 8 Case 2. Left foot showing vestigial big toe.

Histological examination of the bone was normal. Radiological examination showed findings similar to case 1 with absent ossification of the phalanges of the fingers and toes, irregularly thickened cortices of the long bones, and unusual ossification of the cranial vault.

The mother of cases 1 and 2 later gave birth to a normal, healthy male infant, after a pregnancy which was carefully monitored with ultrasound.



Figure 7 Case 2 (brother of case 1). Male fetus at 18 weeks' gestation. Note the vestigial thumbs.

#### CASE 3

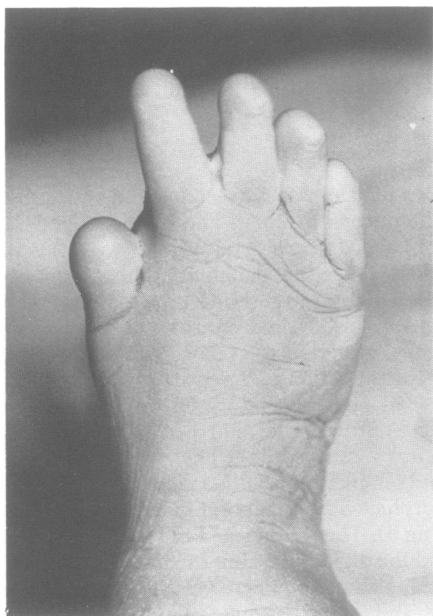
Case 3, a female, was the second child of healthy, non-consanguineous parents. The mother, aged 31, had previously had a miscarriage at 13 weeks' gestation, and then a healthy daughter. The pregnancy was complicated by intrauterine growth retardation and falling oestriols. Delivery was by caesarean section at 39 weeks' gestation for fetal distress and the infant required intubation and ventilation for a short time because of poor respiratory effort. Birth weight was 2018 g (<3rd centile) and head circumference was 29.5 cm (<2nd centile). The skull was abnormally soft and felt like a fluid filled plastic bag. The face was dysmorphic with bitemporal indentations and a small chin (fig 9). The thumbs and big toes were absent (fig 10) and the digits were abnormal with absent nails and terminal phalanges. There were fractures of the right femur and right clavicle. The baby was grossly hypotonic with an absent Moro reflex. There were bilateral cataracts. Calcium, phosphorus, and alkaline

phosphatase were normal and the chromosome complement was 46,XX.

Radiological examination (fig 11) confirmed the presence of fractures. The ribs and diaphyses of the



*Figure 9 Case 3 (sister of case 4). Facial appearance shortly after birth. Note bitemporal indentations and small chin.*



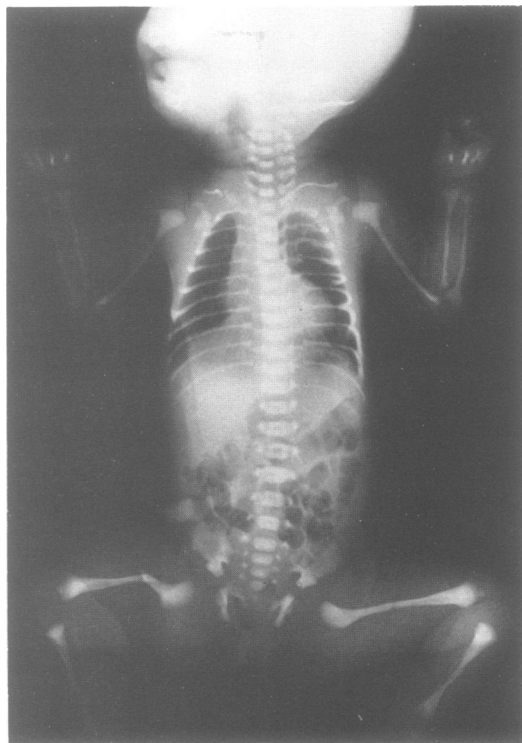
*Figure 10 Case 3. Right foot showing vestigial big toe and hypoplastic nails.*

long bones were slender with irregularly thickened cortices. There were unusual constrictions of the metadiaphyses with abrupt widening at the metaphyses. The first metatarsals and metacarpals were absent and ossification of the phalanges was rudimentary. There was constriction of the iliac bones in the supra-acetabular regions. Similarly, a constriction was present medial to the glenoid fossa of the scapula. The calvarium was poorly mineralised but coarse trabecular ossification was present.

The baby failed to thrive and died at 3 weeks of age. Necropsy showed absence of the occipital bone and the presence of callus at fracture sites. The myocardium was very thick but the heart was otherwise normal, and there was no cerebral malformation.

#### CASE 4

Case 4, a female, was the sister of case 3. She was born at term weighing 2790 g (10th centile) with a head



*Figure 11 Case 3. Radiograph showing fractured right femur and clavicle and slender ribs, clavicles, and diaphyses of long bones, with marked metaphyseal flaring. Absent thumbs. Flared iliac wings with supra-acetabular constrictions laterally. Constrictions also present in medial to glenoid fossae of scapulae. Bone maturation generally retarded.*

circumference of 31.5 cm (2nd centile). Her appearance (fig 12) was similar to her sister's (fig 9), with absence of the right thumb (fig 13), a vestigial left thumb, absence of the nails and terminal phalanges of all fingers, and absent big toes. The skull bones were

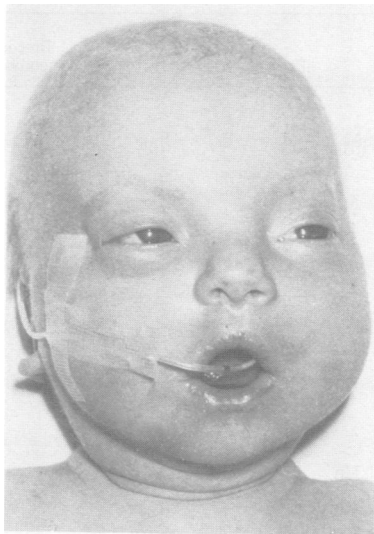


Figure 12 Case 4 (sister of case 3). Facial appearance at 4 weeks.



Figure 13 Case 4. Right hand showing absent thumb and shortening of the fingers.

very soft and the sutures widely separated. Radiological changes were similar to case 3 and there were fractures of both fibulae. Chromosome complement was 46,XX. She failed to thrive and died at 7 weeks.

At necropsy the fissures between the lobes of the lungs were incomplete, and there was incomplete separation of the right and left lobes of the liver. The brain had a normal configuration. Histology of bone showed non-specific changes only.

A subsequent pregnancy was closely monitored with ultrasound and resulted in the birth of a healthy boy.

### Discussion

In the table, the clinical and radiological features in the four cases described above are compared with the eight previously described cases of the Yunis-Varon syndrome, summarised recently by Hennekam and Vermeulen-Meiners.<sup>1</sup> The similarity between the hands and feet, with absence or hypoplasia of the thumbs and big toes and distal aphalangia, was very striking. The facial features were also similar, although our cases did not show the glossoptosis and labiogingival retraction described in the Yunis-Varon syndrome. The craniofacial disproportion and micrognathia, which are features of the Yunis-Varon syndrome, were more marked in our cases 3 and 4 than in cases 1 and 2. The clinical course of our patients was similar to the majority of patients with the Yunis-Varon syndrome, with severe failure to thrive and early death. Features in our patients not previously described in the Yunis-Varon syndrome were the sclerocornea in our case 1, the cataract in case 3, and the CNS malformations in cases 1 and 2.

The radiological findings in the hands and feet were very similar in our cases to those described in the Yunis-Varon syndrome. Our cases showed similar lack of mineralisation of the skull vault in cases 2, 3, and 4. Case 1 showed an unusual coarse trabecular pattern of ossification in the parietal and occipital bones. The pelvic dysplasia in the Yunis-Varon syndrome is described as flattened acetabula and decreased iliac diameters with hip dislocation, although no radiographs of the pelvis in this condition have been published. At least one of our patients had bilateral hip dislocation. Our cases 1, 3, and 4 had flared iliac wings, short sloping acetabula, and unusual supra-acetabular constrictions laterally. Constrictions were also present medial to the glenoid fossae of the scapulae in two of our patients. These findings have not previously been described in the Yunis-Varon syndrome. One of the main distinguishing features was the presence of clavicles in all our patients. Other radiological features in our cases not previously described in the Yunis-Varon syndrome were cortical irregularity, thin diaphyses with flared metaphyses, and pathological fractures.

The radiological changes in our patients resemble those described by Kozłowski *et al*<sup>3</sup> as an autosomal recessive form of precocious osteodysplasia. They reported a brother and sister with normal, possibly consanguineous parents, and a girl from another

family, who all died in infancy with pneumonia. All had prenatal and severe postnatal growth retardation, feeding problems, and failure to thrive. All had rhizomelic shortening of the limbs, with short digits and hypoplastic nails. There were generalised bony

*Summary of clinical and radiological findings.*

	Previous cases of Yunis-Varon syndrome <sup>1</sup>	Present cases				Precocious osteodysplasia <sup>3</sup>		
	n=8 4M/4F	1 M	2 M	3 F	4 F	1 F	2 M	3 F
<i>Clinical</i>								
Case	n=8	1	2	3	4	1	2	3
Sex	4M/4F	M	M	F	F	F	M	F
Birth length <3rd centile	6/7	-	-	-	-	-	+	-
Birth weight <3rd centile	6/8	-	-	+	-	+	+	+
Microcephaly	2/6	-	-	+	+	-	-	-
Wide sutures/fontanelles	8/8	+	+	+	+	+	-	+
Sparse scalp hair	8/8	+	+	+	+	-	-	-
Hypoplastic facial bones	7/7	+	+	-	-	-	-	-
Small eyes	3/5	-	-	+	+	-	-	-
Proptosis	3/5	+	+	+	+	-	-	-
Anteverted nostrils	6/7	+	+	+	+	-	-	-
Short upper lip	8/8	+	+	+	+	-	-	-
Labiogingival retraction	5/5	-	-	-	-	-	-	-
Glossoptosis	2/4	-	-	-	-	-	-	-
Narrow/high arched palate	6/7	+	-	-	-	-	-	-
Micrognathia	8/8	+	+	+	+	+	-	-
Low set/dysplastic ears	8/8	+	+	+	+	-	-	-
Loose skin in neck	2/2	+	-	+	+	-	-	-
Absent nipples	2/8	-	-	-	-	-	-	-
External genital anomalies	2/5	Hp	-	-	-	-	-	-
Bilateral hip dislocation	4/6	+	-	-	-	-	-	-
Bilateral simian crease	2/5	+	+	+	+	-	-	-
Absent thumbs	7/7	+	+	+	+	-	-	-
Short, pointed fingers	7/7	+	+	+	+	-	+	+
Nail hypoplasia/agenesis	6/8	+	+	+	+	+	+	+
Absent halluces	8/8	+	+	+	+	-	-	-
Short, pointed toes	6/8	+	+	+	+	-	-	-
Death in neonatal period	6/8	4/12	TOP	3/52	7/52	>9/12	9/12	11/12
Sclerocornea		+	-	-	-	-	-	-
Cataract		-	-	+	-	-	-	-
CNS malformation		+	+	-	-	-	-	+
<i>Radiological</i>								
Calvarial dysostosis	5/5	+	+	+	+	-	-	-
Wide sutures	5/5	+	+	+	+	-	-	-
Craniofacial disproportion	5/5	+	+	+	+	-	-	-
Micrognathia	6/6	+	+	+	+	+	-	-
Absent clavicles	6/6	-	-	-	-	-	-	-
Absent sternal ossification	4/4	-	-	-	-	-	-	-
Pelvic dysplasia (flattened acetabula, decreased iliac diameter)	3/3	-	-	-	-	-	-	-
Pelvic dysplasia (short, sloping acetabula, flared iliac wings, supra-acetabular constrictions)		+	-	+	+	+	-	-
Hip dislocation	3/4	+	-	-	-	-	-	-
Agenesis of thumbs	5/5	+	+	+	+	-	-	+
Agenesis of distal phalanges of fingers	4/5	+	+	+	+	-	-	+
Agenesis of middle phalanges of fingers	4/5	H	H	H	H	-	-	+
Agenesis of first metatarsals	5/6	+	+	+	+	-	-	H
Hypoplasia of hallucal phalanges	5/5	+	+	+	+	-	-	+
Agenesis of distal phalanges of toes	3/3	+	+	+	+	-	-	+
Abnormal scapulae		+	+	+	+	-	-	+
Coxa valga		+	-	-	-	+	+	+
Flared metaphyses		+	+	+	+	-	+	+
Submetaphyseal constriction		+	+	+	+	-	+	+
Thin, constricted diaphyses		+	+	+	+	-	+	+
Delayed bone maturation		+	+	+	+	+	+	+
Pathological fractures		-	-	+	+	-	-	-

Hp=hypospadias, H=hypoplasia, TOP=termination of pregnancy.

changes including broad, poorly modelled diaphyses and irregularity of the cortex of the long bones, poorly ossified phalanges, narrow supra-acetabular regions, coxa valga, slender, irregular ribs, and thin tapered clavicles. Our cases differed from those of Kozlowski *et al*<sup>3</sup> in that ours showed more marked thinning of the calvarium, with more severe hypoplasia of the thumbs and big toes, and the facial dysmorphism in our cases was more marked. The features of our patients and those of Koslowski *et al* are compared in the table.

Severe osteodysplasty has also been described in severely affected males born to mothers with Melnick-Needles syndrome,<sup>6-10</sup> which is thought to be inherited either as an X linked dominant or an autosomal sex limited dominant trait. There is considerable heterogeneity in severely affected males. Features which may be present are oligohydramnios, prominent eyes, hypertelorism, sclerocornea, cleft palate, small chin, chest deformity, omphalocele, urinary tract abnormality, abnormal genitalia, hypoplastic thumbs and big toes, and hypoplastic nails.

Radiologically there may be a thin calvarium with stellate ossification pattern, small mandible, spinal deformity, abnormality of the ribs and shoulder girdle, talipes, curved long bones with cortical irregularities, metaphyseal flaring, and soft tissue calcification. Although our case had some features in common with these cases, the pattern of inheritance would not be compatible with this diagnosis, since the mother of cases 1 and 2 was normal, and cases 3 and 4 were female. However, it is interesting that the description of the eye abnormality in the case of Theander and Ekberg<sup>6</sup> resembles our case 1, and peripheral sclerocornea has also been reported in a 10 year old girl with Melnick-Needles syndrome.<sup>11</sup>

The occurrence of the Yunis-Varon syndrome in two further sib pairs provides further evidence for autosomal recessive inheritance of this disorder. Our

cases show that absence of the clavicles is not an invariable feature of this condition, that abnormalities of the eyes and central nervous system may occur, and that striking radiological features may be present in addition to those previously described. These changes resemble the precocious type of osteodysplasia, but the relationship between this condition and the Yunis-Varon syndrome requires further elucidation.

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