Congenital heart malformation in Yunis-Varón syndrome

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Abstract

We describe a male infant with Yunis-Varón syndrome who has tetralogy of Fallot. This appears to be the first case of Yunis-Varón syndrome associated with congenital heart malformation.

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In 1980, Yunis and Varón¹ reported five children from three Colombian families with sparse hair, cleidocranial dysostosis, severe micrognathia, bilateral absence of the thumbs and first metatarsal bones, and distal aphalangia. All five children died before the age of 10 weeks. No additional abnormalities were found at necropsy in three children but in a fourth there was tracheal, laryngeal, and pulmonary hypoplasia. Chromosome studies in two of the children were normal. Yunis and Varón¹ suggested autosomal recessive inheritance since sibs of both sexes were affected, the parents were normal, and there was consanguinity in two of three families.

Since the original report, seven further cases have been described.²⁻⁵ In 1983, Hughes and Partington² reported a mildly affected case, adding the features of prenatal and postnatal growth deficiency, prolonged survival, short stature, and mental retardation to the clinical picture. Since that report, a further six cases have been described, including another report by Partington³ of one boy with the additional features of mild hypertelorism, midfacial hypoplasia, premature loss of deciduous teeth, dry skin, one foot smaller than the other, and cardiomyopathy. Garrett *et al*⁴ described cerebral malformation, sclerocornea, cataracts, flared metaphyses, and pathological fractures as new features of the syndrome.

Yunis-Varón syndrome appears to be a generalised disorder with variable effects on growth and development of the skeletal, ectodermal, central nervous, and cardiovascular systems. We report another case, which adds congenital cardiac malformations to the known features of this syndrome. In addition we review the neurological findings and discuss their possible implications.

Case report

The male proband was the first child born to unrelated Anglo-Saxon parents at 36 weeks' gestation after a normal pregnancy, labour, and delivery. Apgar scores were 4 and 6 at one and five minutes respectively. Birth weight was 2630 g (10th to 50th centile), length 44 cm (<10th centile), and head circumference 31 cm (<10th centile). He was tachypnoeic from birth and had periods of desaturation

necessitating oxygen administration in the first few days of life. Acyanotic tetralogy of Fallot was diagnosed by echocardiography. There was no family history of congenital heart disease. The child was hypotonic and fed poorly necessitating gavage feeding.

Craniofacial features (figs 1 to 4) included redundant posterior neck skin, a flat occiput, prominent parietal bossing, bifrontal narrowing, fine, sparse scalp hair, low set and abnormally shaped ears, hypoplastic supraorbital margins giving the impression of mild proptosis, puffy upper eyelids, epicanthic folds, upward slanting palpebral fissures, a beaked nose, mild micrognathia, thin lips, and an upper anterior gingivolabial fold. Funduscopy showed anomalous take off of the retinal vessels from each optic disc. There was distal digital hypoplasia of the thumbs, index, and little fingers (fig 5). The palmar creases were abnormal with bilateral transverse palmar creases and prominent creases perpendicular to the transverse crease. The big toes were held in a cocked up position and there was distal phalangeal hypoplasia (fig 6). He had undescended testes, hypoplastic nipples, a left dislocated hip, and profound hypotonia.

Skeletal radiographs (figs 7 to 10) showed central defects in both clavicles, winged and

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Figure 1 The proband aged 6 months showing sparse hair, upward slanting palpebral fissures, and epicanthic folds.

Figure 2 The proband aged 6 months showing beaked nose, abnormally shaped ears, and mild micrognathia.

Figure 3 The proband aged 12 months.

hypoplastic scapulae, a mild kyphosis at the cervicothoracic junction, broad sacrosciatic notches, failure of ossification of the pubic bones and of the symphysis pubis, and left hip dislocation. The distal phalanx of the thumb, index, and little fingers were hypoplastic, the first metacarpal was short, and there was hypoplasia of the middle phalanges of both little fingers with clinodactyly. There was hypo-

Figure 4 The proband aged 12 months.

Figure 5 View of the hand showing distal digital hypoplasia of the thumb, index, and little fingers and clinodactyly of the little finger.

Figure 6 View of the toes showing distal phalangeal hypoplasia.

plasia of the first metatarsal and proximal phalanx of both great toes and of the distal phalanges of the toes.

A Nissen fundoplication and gastrostomy were performed at 5 months of age because of continued poor feeding. At the age of 11½ months he had become microcephalic and developmental progress was assessed at a 3 to 4 month level. Growth was retarded, with both height and weight remaining well below the 3rd centile throughout the first year. At that time the cardiac lesion had not required treatment because there was a net left to right shunt and the patient had not experienced any cyanotic attacks.

Figure 7 Chest radiograph showing hypoplasia of the clavicles.

Figure 8 Radiograph of the pelvis.

Figure 9 Hand radiograph showing distal phalangeal hypoplasia.

Figure 10 Foot radiograph showing distal phalangeal hypoplasia.

Cranial ultrasound (fig 11) showed a large interthalamic adhesion and mild dilatation of the fourth ventricle associated with hypoplasia of the inferior cerebellar vermis. Ultrasound of the urinary tract showed minor dilatation of the renal pelves.

Chromosome studies showed a normal male karyotype, 46,XY. Biochemical studies undertaken included serum creatine kinase, serum very long chain fatty acids and amino acids, plasma lactate and pyruvate, lysosomal enzymes, and urinary amino and organic acids. All results were normal.

Discussion

The main characteristics of the Yunis-Varón syndrome include prenatal and postnatal growth deficiency, craniofacial disproportion, agenesis or hypoplasia of the clavicles, digital anomalies especially extreme hypoplasia of the first rays, and, usually, death in the first weeks of life. The clinical and radiological features of our case are compared with the previously reported patients with Yunis-Varón syndrome

Figure 11 Cranial ultrasound showing interthalamic adhesion and hypoplasia of the inferior cerebellar vermis.

in tables 1 and 2 respectively. The facial features were strikingly similar to those of previous cases, although our case lacked the craniofacial disproportion, wide sutures and fontanelles, glossoptosis, and narrow/high arched palate described in most other cases. The pattern of abnormalities of the hands and feet was characteristic although less severe than in some others. The clinical course of our patient is similar to that of most cases of Yunis-Varón syndrome with severe failure to thrive and marked psychomotor delay dominating the clinical picture. Survival has been possible as a result of gavage feeding.

A congenital heart malformation, present in our patient, has not been described before in Yunis-Varón syndrome. Partington³ reported dilated cardiomyopathy in one patient and case 3 of Garrett *et al*,⁴ who died at the age of 3 weeks, was found to have myocardial hypertrophy at necropsy.

Mental retardation, hypotonia, and hypertonia have all been described in the Yunis-Varón

syndrome and structural brain abnormalities are likely to have contributed to these features in some cases. Garrett *et al*⁴ provided the first description of central nervous system malformations in two patients with Yunis-Varón syndrome. One patient with absence of the olfactory bulbs and tracts (arhinencephaly) and a hamartomatous lesion of the lateral ventricle had severe weakness and hypotonia and died of pneumonia at the age of 4 months. In that case, neuropathological study confirmed neuronal loss and vacuolisation in cells of the cerebral cortex, dentate nuclei, basal ganglia, olives, and anterior horn cells. The second case, a fetus, had agenesis of the corpus callosum and dilatation of the lateral ventricles on ultrasound at 18 weeks' gestation. The pregnancy was terminated and no description of the histological appearance of the brain was provided. Our patient had a developmental abnormality of the cerebellar vermis and a large interthalamic adhesion, neither of which have been previously described in the Yunis-Varón syndrome. It is clear that various brain malformations can occur in Yunis-Varón syndrome but more detailed neuropathology will be needed if the mechanism of severe central nervous system dysfunction is to be understood.

Yunis-Varón syndrome is one of a small number of defined multiple congenital anomaly syndromes in which congenital clavicular hypoplasia/agenesis occurs.⁵ This finding suggested the diagnosis in our patient and prompted a full skeletal survey which allowed confirmation. Garrett *et al*⁴ reported four patients with Yunis-Varón syndrome who did not have absent or hypoplastic clavicles. These patients had metaphyseal and diaphyseal abnormalities reminiscent of severe precocious osteodysplasty as described by Kozłowski *et al*⁶ and two had pathological fractures. Our patient had no skeletal features suggestive of osteodysplasty.

The presence and equal severity of the syndrome in sibs of both sexes, absence of reports of the syndrome in more than one generation, and consanguinity in three of the nine families now described point to an autosomal recessive mode of inheritance. Hennekam and Vermeulen-Meiners⁷ reported shortening of the thumbs and distal phalanges in the mother of a patient but no such anomalies have been found in the parents of the other described patients. Radiological investigations were not performed, however, so it remains unclear whether these anomalies could occur more often. Hand radiographs of the parents of our case were normal.

This report of another patient with the Yunis-Varón syndrome adds congenital heart disease and new central nervous system malformations to the growing list of features accompanying the condition.

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Table 1 Clinical features of Yunis-Varón syndrome.

	Previous cases of Yunis-Varón syndrome (n = 12)	Present case
Sex	6M/6F	M
Birth length < 3rd centile	6/8	—
Birth weight < 3rd centile	7/9	—
Microcephaly	4/10	+
Wide sutures/fontanelles	12/12	—
Sparse scalp hair	11/11	+
Hypoplastic facial bones	9/9	+
Small eyes	5/7	—
Proptosis	7/9	—
Anteverted nostrils	10/11	+
Short upper lip	12/12	—
Labiogingival retraction	5/9	+
Glossoptosis	2/8	—
Narrow/high arched palate	7/8	—
Micrognathia	12/12	+
Low set/dysplastic ears	12/12	+
Loose neck skin	5/6	+
Absent nipples	2/12	Hypoplastic
External genital anomalies	3/9	+
Bilateral hip dislocation	5/8	+
Bilateral simian crease	6/9	+
Absent/hypoplastic thumbs	11/11	+
Short pointed fingers	11/11	+
Nail hypoplasia/agenesis	10/12	+
Absent/hypoplastic halluces	12/12	—
Short, pointed toes	10/12	+
Death in neonatal period	7/9	—
Sclerocornea	1/4	—
Cataract	1/4	—
CNS malformation	2/4	+
Cardiomyopathy	1/12	—
Structural cardiac malformation	0/12	+

Table 2 Radiological features of Yunis-Varón syndrome.

	Previous cases of Yunis-Varón syndrome (n = 12)	Present case
Calvarial dysostosis	9/9	—
Wide sutures	8/9	—
Craniofacial disproportion	9/9	—
Micrognathia	10/10	+
Absent/hypoplastic clavicles	6/10	+
Abnormal scapulae	2/2	+
Absent sternal ossification	4/4	—
Pelvic dysplasia	6/7	+
Hip dislocation	4/6	+
Coxa valga	2/2	—
Agenesis/hypoplasia of thumbs	9/9	+
Agenesis/hypoplasia of distal phalanges of fingers	8/9	+
Agenesis/hypoplasia of middle phalanges of fingers	8/9	+
Agenesis/hypoplasia of first metatarsals	9/10	+
Hypoplasia of hallucal phalanges	9/9	+
Agenesis/hypoplasia of distal phalanges of toes	7/7	+
Flared metaphyses	4/4	—
Submetaphyseal constriction	3/4	—
Thin, constricted diaphyses	4/4	—
Delayed bone maturation	2/2	—
Pathological fractures	2/4	—

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- 3 Partington MW. Cardiomyopathy added to the Yunis-Varón syndrome. *Proc Greenwood Genetic Center* 1988;7:224-5.
- 4 Garrett C, Berry AC, Simpson RH, Hall CM. Yunis-Varón syndrome with severe osteodysplasty. *J Med Genet* 1990;27:114-21.
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