Case reports

Neonatal Marfan syndrome with congenital arachnodactyly, flexion contractures, and severe cardiac valve insufficiency

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Abstract

We describe a male neonate with severe arachnodactyly, hypermobility of the fingers, flexion contractures of elbows, wrists, hips, and knees, micrognathia, crumpled ears, rockerbottom feet, loose redundant skin, and ocular abnormalities. Severe cardiac valve insufficiency and aortic dilatation resulted in cardiac failure and death 20 hours after birth. This case represents the severe end of the clinical spectrum of Marfan syndrome. As similar patients have been reported, they may represent a separate mutation.

Marfan syndrome is an autosomal dominant disorder mainly affecting the skeletal system (arachnodactyly, tall stature, anterior chest and vertebral column deformities), the cardiovascular system (dilatation or dissection of the aorta and mitral valve prolapse), and the ocular system (ectopia lentis and myopia).[1 2]

Beals and Hecht[3] noticed that some of their patients with Marfanoid characteristics also showed congenital contractures, and they identified similar patients in published reports, including the original patient described by Marfan.[4] This led to the delineation of a new syndrome, congenital contractural arachnodactyly (CCA) or Beals syndrome (McKusick 12105), which is characterised by congenital contractures of the elbows, knees, hips, and fingers (camptodactyly), arachnodactyly with ulnar deviation of the fingers, kyphoscoliosis, adducted thumbs, crumpled ears, micrognathia, knobbly appearance of the joints owing to absence of subcutaneous fat, and muscle hypoplasia (especially of the calf muscles).[3 5–7] In view of the similarities between the Marfan and Beals syndromes it has been suggested that they might represent variations of the same genetic entity.[2]

At one end of a wide clinical spectrum there are mildly affected patients who can be difficult to diagnose. At the other end there are several patients with severe prenatal clinical manifestations. This case report represents one of the rather small group of severely affected children with lethal outcome before the age of 2 years.

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Case report

HISTORY

The male proband was born at 39 weeks' gestation. The mother was a healthy, 28 year old primigravida. She was using oral contraceptives at the time of conception. The father was an unrelated 41 year old man with a healthy 21 year old daughter from a former marriage. He was on interferon treatment for hepatitis B. This pregnancy had been uneventful until fetal cardiomegaly and aortic dilatation were noticed on routine ultrasonography at 35 weeks' gestation. Therapeutic action was not undertaken. Immediately after spontaneous delivery the neonate had to be resuscitated, intubated, and ventilated artificially. Owing to severe impairment of the cardiovascular circulation the child died 20 hours after birth.

PHYSICAL EXAMINATION

At examination shortly after birth, OFC was 36·5 cm (between the 50th and 97th centile), weight was 3400 g (50th centile), length was 55 cm (above the 97th centile), and span was approximately 50 cm. Birth length and span were probably underestimated as measurement was impaired by joint contractures (knees, hips, elbows, wrists). The child showed several dysmorphic features. Severe arachnodactyly was present in both hands and feet (figs 1 and 2). Middle finger length was 3·5 cm and palm length 4 cm on both sides. Foot length was 9·0 cm (right) and 9·2 cm (left) (50th centile=7·9 cm). The finger joints showed hyperlaxity. Bilateral rockerbottom feet with long toes and symmetrical clinodactyly of the third toes and to a lesser extent the fourth toes were present (figs 2 and 3). Flexion contractures of both hips, elbows, knees, and wrists were obvious (fig 1). The skin was loose and abundant, creating a senile look to the facies. The ears were crumpled with hypoplastic cartilage of the helix (fig 4). Absence of subcutaneous fat and hypoplasia of the calf muscles (figs 1 and 2) were noticed. The sclerae had a slightly blue discolouration. There were no abnormalities of the nails or hair and, apart from bilateral cryptorchidism, the external genitalia appeared normal.

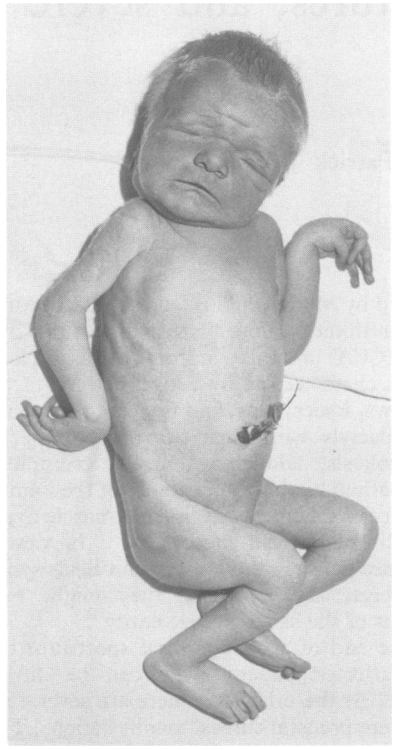

Figure 1 Patient one hour after death. Note senile appearance, arachnodactyly, contractures of elbows, hips, wrists, and knees, thumb adduction, redundant, loose skin and knobbly appearance of joints owing to absence of subcutaneous fat and muscle hypoplasia.

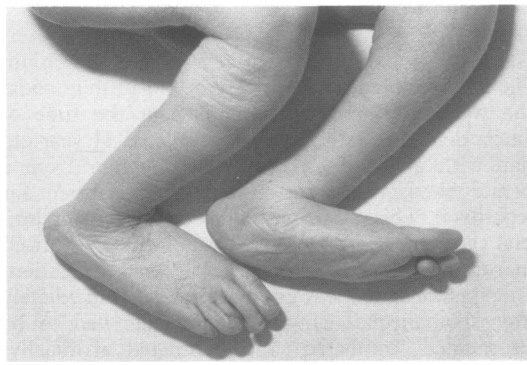

Figure 2 Rockerbottom feet with arachnodactyly, overlapping toes, and hypoplasia of calf muscles.

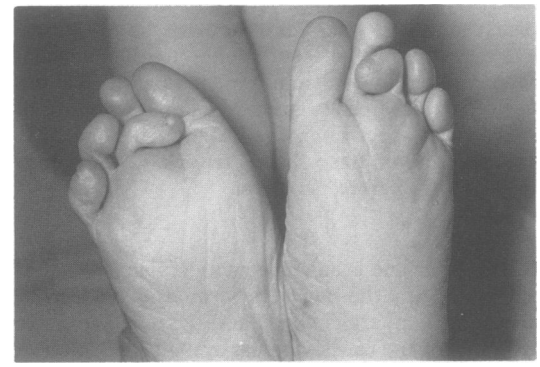

Figure 3 Bilateral clinodactyly of third toe.

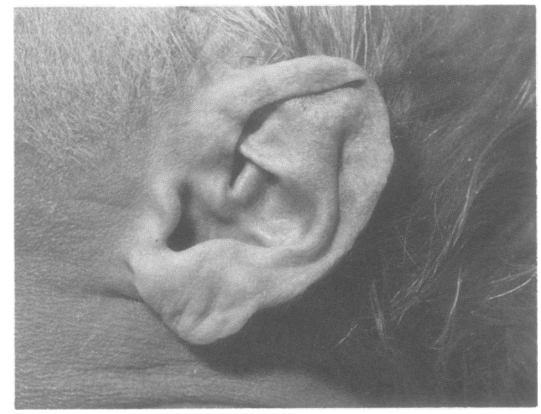

Figure 4 Crumpled ear with hypoplastic cartilage.

CARDIOLOGICAL EXAMINATION

The child's heart was hyperactive and a diffuse thrill could be felt over the whole praecordium. A systolic-diastolic mumur was heard radiating into the neck. Signs of marked dilatation of both atria and biventricular hypertrophy were noticed on an electrocardiogram. Radiological examination of the chest showed extreme cardiomegaly with the heart filling almost the whole thorax. On echocardiography all heart chambers were found to be grossly dilated. The pulmonary and aortic roots were particularly large with aneurysmal dilatation of the left coronary artery. There was marked prolapse of both mitral and tricuspid valves. Doppler examination showed severe insufficiency of all four heart valves.

RADIOLOGICAL EXAMINATION

A skeletal survey showed arachnodactyly of all fingers and toes, clinodactyly of the third and fourth toes, and flaring of the metaphyses of the long bones, especially of the humerus and the femur.

NECROPSY STUDIES

Necropsy showed a grossly enlarged heart with dilatation of all four heart cavities. The heart valves were very dysplastic and showed signs of prolapse (fig 5). The chordae tendinae were abnormally inserted and were too long. Severe dilatation of the dysplastic aorta and pulmonary artery caused failure of the valve leaflets to coapt (fig 5). Microscopic examination of the heart showed pronounced myxoid degeneration of the arterial wall with presence of lacunae and fragmentation of elastic laminae. There was myxoid degeneration of the atrioventricular valves. The myocardium showed interstitial oedema with dilated vessels and sinusoids between the muscle bundles.

Ophthalmological studies showed a bluish colour of the anterior sclerae. Both sclerae were thinner than normal and showed intercellular gaps with reduced cohesion between collagen fibres. Partial absence of the musculus dilator pupillae and amaurotic cylindrical epithelia were found in the periphery of the iris. The corneae and lenses were normal. The ciliary processes were reduced in number and hypoplastic. Electron microscopic studies of the aortic wall and skin showed collagen fibres with great variation in width and a reduced amount of elastin filaments.

Neuropathological examination was normal, except for atypical polymicrogyry of the brain. Further macroscopic and microscopic investigations of the other organs were all normal.

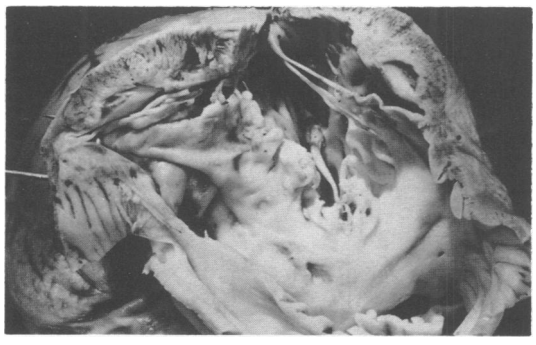

Figure 5 Dissected heart showing severe valve dilatation and prolapse.

LABORATORY STUDIES

Chromosome analysis showed a normal male karyotype, 46,XY. Homocystine concentration in urine and blood was normal. Biochemical collagen studies of skin fibroblasts were all normal. This included ratios of collagen types I, III, and V, and electrophoretic mobility of α1(I), α2(I), and α1(III) chains (Dr B Steinmann, Zürich).

EXAMINATION OF THE PROBAND'S PARENTS

Both parents were examined for the presence of Marfanoid features. The father's height was 1·76 m (25th centile) and the mother's was 1·71 m (50th centile). Physical examination did not show arachnodactyly, dolichostenomelia, or other features of the Marfan syndrome. Radiological examination of the spine, thorax, and extremities, including measurement of the metacarpal index, were normal in both parents. Ophthalmological examination showed slight myopia and congenital nystagmus in the mother and colour blindness (red-green pigment) in the father. Heart auscultation, electrocardiogram, and echocardiographic examination were normal in the father.

In the mother a 2/6 systolic murmur was heard on auscultation. While the electrocardiogram was normal, the echocardiographic examination showed a systolic prolapse of the anterior mitral valve.

Discussion

Severe cardiovascular manifestations resulting in cardiac failure and death in the neonatal period, as in our patient, are unusual in Marfan syndrome.[8–10] Reviewing published reports we identified only a small number of patients with severe neonatal cardiovascular manifestations.[10–28] Table 1 shows a very similar pattern of symptoms in all these patients. The majority of them had severe cardiovascular abnormalities leading to death in the neonatal period, arachnodactyly, a combination of joint contractures and joint laxity, and crumpled ears. Some of these features are infrequent in the Marfan syndrome (contractures, micrognathia, and crumpled ears). Several patients

Table 1 Marfanoid patients with severe cardiovascular manifestations in the neonatal period.

Reference		Cardiovascular abnormality	Arachno-dactyly	Joint hypermo-bility	Congenital contractures	Crumpled ears	Loose skin	Microg-nathia	Anterior chest deformity	Pulmonary emphysema	Ocular abnormalities	Age at death	Sporadic occurrence
28		+	+		+	+		+	−		+	10 mth	+
10		+	+			+			+		+	5 mth	+
24		+	+	+		+	+	+	−	+	+	2½ mth	
19	Case 1	+	+		+	+		+				8 mth	
	Case 2	+	+		+	+		+			−	26½ mth	+
25	Case 1	+	+		+	+		+	+		+	3 mth	+
16		+	+	+								Birth	+
18		+	+	+	+	+		+			−	3 mth	+
21		+	+	+	+							3 d	+
12		+	+		−		+	+				Birth	+
20		+	+	+		+	+		+		−	4 d	
11		+	+		+	+	+					8 mth	
27		+	+		+	+		+	−		+	6 mth	+
14		+	+	+	+	+				+		10 d	
15	Case 1	+	+	−	+	+	+		+	+	+		+
	Case 2	+	+	+	+		+		+	+	+		+
	Case 3	+	+	+	+	+	+		+	+	+	21 mth	+
	Case 4	+	+	−	−	+	+	+	+	+	−		+
22		+	+	+	+				+			4 mth	+
17	Case 1	+	+	+	+	+	+	+		+	+	21 mth	+
	Case 2	+	+	+	−	+	+	+	+	−	+	3½ mth	+
Present case 1990		+	+	+	+	+	+	+	−		+	1 d	+
Total	22 cases	22/22	22/22	12/22	15/22	15/22	11/22	12/22	9/22	7/22	10/22	Average	18/22
Morse *et al*[23]		16/20	+	+	16/20	?	?	+	+		+	6·1 mth	
												3/22	19/22
												<24 mth	
												2/22	
												>24 mth	

Table 2 Cardiovascular abnormalities in the neonatal period in Marfanoid patients.

Reference		Mitral valve abnormalities	Tricuspid valve abnormalities	Aortic abnormalities	Other
28		Prolapse	Prolapse	Dilatation, cystic media necrosis	Cardiomegaly
10		Dilatation	Dilatation	Cystic media necrosis	Cardiomegaly
24		Insufficiency		Aortic root dilatation, cystic media necrosis	
19	Case 1	Dilatation	Dilatation	Dilatation, cystic media necrosis	Cardiomegaly
	Case 2	Dilatation	Dilatation	Dilatation	Cardiomegaly
25		Insufficiency			Cardiomegaly
16		Dilatation	Dilatation	Dilatation, valve insufficiency, cystic media necrosis	Cardiomegaly
18		Prolapse	Prolapse	Dilatation	Patent foramen ovale, cardiomegaly
21		Prolapse	Valve insufficiency	Patent ductus arteriosus	Cardiomegaly atrial septal defect
12		Dilatation	Dilatation	Cystic media necrosis	Cardiomegaly
20		Insufficiency, dilatation	Dilatation	Dilatation, cystic media necrosis	Cardiomegaly
11		Prolapse	Prolapse	Dilatation, cystic media necrosis	Cardiomegaly
27		Prolapse	Prolapse		Cardiomegaly
14		Prolapse	Prolapse	Dilatation	Cardiomegaly
15	Case 1	Prolapse	Prolapse	Dilatation	
	Case 2	Prolapse	Prolapse	Dilatation	Cardiomegaly
	Case 3	Prolapse	Prolapse	Dilatation	Cardiomegaly
	Case 4	Prolapse	Prolapse		
22		Prolapse	Insufficiency	Dilatation	Cardiomegaly
23		Prolapse	Prolapse	Dilatation	Cardiomegaly (chamber enlargement)
17	Case 1	Prolapse	Prolapse	Dilatation	Atrial enlargement
	Case 2	Prolapse, regurgitation	Prolapse, regurgitation	Dilatation	Cardiomegaly
Present case		Prolapse, dysplastic valve	Prolapse	Dilatation	Cardiomegaly

also showed loose, redundant skin, micrognathia, anterior chest deformity, and ocular abnormalities. In contrast with the patient of Tamminga *et al*,[27] who showed hypoplasia of the cerebral white matter and spinal axonopathy, our patient had no neuropathological abnormality. The cardiovascular anomalies mainly affected the mitral and tricuspid valve and the aorta (table 2).

Most of the Marfan patients with severe neonatal cardiovascular manifestations were sporadic cases (table 1). Only the patients of Chemke *et al*[13] and Schollin *et al*[26] were familial cases, but they are unusual as they were homozygous for two mutant Marfan genes, and severe expression of dominant disease in the homozygous state has also been described for achondroplasia, hypercholesterolaemia owing to LDL receptor defects, and autosomal dominant brachydactyly.

Our patient was also a sporadic case. However, mitral valve prolapse was found in his mother and therefore the possibility of a minor expression of the Marfan gene was considered. However, mitral valve prolapse is a non-specific symptom and is found in the normal population, especially in women, with a relatively high frequency (6·3%).[29] As such, the presence of mitral valve prolapse alone was insufficient to sustain the diagnosis of Marfan syndrome in the mother.

Reviewing published reports we found 18 out of 22 cases with severe neonatal cardiovascular manifestations to be sporadic, while no information was available for the remaining four cases. This is consistent with the findings of Morse *et al*,[23] who presented 22 neonates with Marfan syndrome diagnosed before the age of 3 months. In this series only three out of 22 cases were familial. As detailed clinical information was not available on the three familial cases, it is possible that they did not have severe cardiovascular manifestation which was the selection criterion in the group of patients listed in table 1. Combining these results, 37 of 44 cases with neonatal manifestations were sporadic. This is remarkable since one would expect only 25% of patients with Marfan syndrome to represent new mutations.[2 21 22] Also, the presence of severe neonatal manifestations not usually seen in classical Marfan syndrome and the similar clinical pattern of the patients suggests genetic heterogeneity.

Since the molecular basis of Marfan syndrome is still unknown, it is unclear at present whether different mutations in one 'Marfan gene' or whether mutations in distinct gene loci are responsible for the disease. Gross *et al*[17] stated that patients with severe neonatal Marfan syndrome represent a distinct form of the syndrome.

The inheritance pattern of this possibly separate entity in the Marfanoid syndromes is unlikely to be autosomal recessive given the absence of affected sibs (the only sib pair were identical twins[19]) and the lack of consanguinity between the parents. X linked recessive inheritance can also be excluded because of the equal sex distribution among the patients. Most likely, they represent new dominant mutations, as appears to be the case for the majority of type II OI patients.

Although a few reports have suggested that abnormalities of collagen[30] or elastin fibre components[31] are involved in the pathogenesis of Marfan syndrome, extensive linkage studies with candidate gene loci, such as the fibrillar collagen genes,[32 33] do not support the biochemical findings. Further information at the molecular level will be needed to confirm whether this subgroup of severe neonatal Marfan patients indeed represents a separate genetic entity.

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