'Little Leopard' Syndrome

Description of 3 Cases and Review of 24

DOUGLAS PICKERING,* BERNARD LASKI, D. C. MACMILLAN†, and VERA ROSE

From the Department of Cardiology, The Hospital for Sick Children, Toronto, Ontario, Canada; and the Radcliffe Infirmary, Oxford

Pickering, D., Laski, B., MacMillan, D. C., and Rose, V. (1971). *Archives of Disease in Childhood*, 46, 85. 'Little leopard' syndrome. Description of 3 cases and review of 24. Three cases of the 'Little Leopard' syndrome are described; its features are short stature, lentigines, electrocardiographic and ocular defects, pulmonary infundibular stenosis, abnormal genitalia, mental retardation, and deafness. The published material is reviewed, and the cardiac and electrocardiographic abnormalities are described in detail.

The word 'leopard' was first applied as a mnemonic by Gorlin, Anderson, and Blaw (1969) to the syndrome of multiple lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis and other congenital heart defects, abnormalities of genitalia and reproductive physiology, retarded growth, and deafness. The condition is inherited as an autosomal dominant of variable penetrance.

Lentigines are small dark-brown spots which may be present at birth or appear shortly after. Their pathognomonic feature is the combination of a saw-tooth appearance of the dermal epidermal junction combined with a single layer of pigment cells which contrasts with the nests of the cells that occur in a naevus. They usually appear earlier than freckles, contain a greater number of melanocytes per unit of skin area, and do not increase in number with exposure to sunlight.

This paper reports 3 cases, 2 seen at The Hospital for Sick Children, Toronto, and one at the Radcliffe Infirmary, Oxford, together with a review of the literature, in which it appears that while a number of the children are retarded physically, a significant proportion are also retarded mentally. We have therefore altered the meaning of the 'r' in 'leopard' to represent retarded mentally.

Case Histories

Case 1. A previously healthy 5-year-old boy was found, during a routine medical examination, to have a heart murmur. His growth and development had been slower than that of his sibs. He was admitted to hospital at 8 years of age because of an increasing number of brownish spots developing on his skin during the preceding year. On physical examination his height, weight, and head circumference were on the 60th centile. He was covered with multiple pigmented lesions and had a bulging left praecordium (Fig. 1a). There was a blowing pansystolic murmur, grade 2/4 at the apex conducted to the axilla, and a grade 2/4 rumbling mid-diastolic murmur at the apex. No other abnormality was noted. Biopsy of a skin lesion showed the sharply localized area of hyperpigmentation in the basal layers of the epidermis and the overlying prickle-cells, characteristic of a lentigo. X-ray of the abdomen showed calcification of the right adrenal gland but an intravenous pyelogram was normal. Skeletal maturation, skull x-rays, protein-bound iodine, fasting blood sugar, Hb, WBC, differential, 17 ketosteroids, ASO titre, electrolytes, urine, and adrenal stimulation tests were all normal. The electrocardiogram showed sinus rhythm and left axis deviation with an anticlockwise loop and left ventricular and probably left atrial hypertrophy (Fig. 1b). Chest x-ray showed a normal heart size and normal pulmonary vascularity. A diagnosis of mitral incompetence with ostium primum atrial septal defect was made. However, on right-sided cardiac catheterization no evidence of right-to-left shunt was found. The patient was discharged home without specific treatment.

At 12 years of age the boy was doing poorly in school.

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†Present address: Radcliffe Infirmary, Oxford, England.

FIG. 1.—Case 1. (a) Front view. (b) ECG shows left ventricular hypertrophy and left axis deviation.

He had developed bilateral ptosis. His testicles were undescended and could not be manipulated into the scrotum. Skeletal maturation was retarded. His IQ was 90 and his verbal ability significantly low. At this

time he was treated unsuccessfully with chorionic gonadotrophin for undescended testes.

He was admitted again at 13 years of age for bilateral orchidopexy and left herniorrhaphy. At this time his

FIG. 2.—Case 2. (a) ECG shows right ventricular hypertrophy and T

height and weight were below the 3rd centile. The lentigo profusa had increased to cover his entire body. Cardiothoracic ratio was increased slightly over that found on the previous admission. The ECG was unchanged. Cardiac catheterization and laevocardiogram showed moderate mitral incompetence. The laevocardiogram was reviewed again following a report by Moynahan (1970) of hypertrophic obstructive cardiomyopathy (HOCM) in these cases, and showed probable subaortic stenosis, suggesting that the mitral incompetence was secondary to the HOCM. Audiology showed a presbycusis type of curve suggesting cochlear involvement. A bilateral orchidopexy and left herniorrhaphy were carried out and the boy discharged home.

Case 2. A symptom-free 2-year-old boy was referred to The Hospital for Sick Children, Toronto, because of a systolic murmur discovered during the course of a respiratory tract infection. His physical development was normal. No freckles or pigmentation were remarked on at that time. There was a grade 2/4 ejection systolic murmur maximal in the 3rd left intercostal space at the left sternal edge. Chest x-ray was normal. Electrocardiogram showed sinus rhythm, axis $+300^\circ$, and right ventricular hypertrophy with an anticlockwise loop and T wave inversion over the left ventricular leads (Fig. 2a). Cardiac catheterization showed mild infundibular pulmonary stenosis. The patient was treated for otitis media and pharyngitis and discharged home.

He was readmitted to hospital 8 years later at the age of 10 for surgical correction of a squint. His lateral canthi were noted to be 4 mm lower than the medial

canthi. By the age of 12 years he was covered with multiple lentiginous spots (Fig. 2b and c).

He was attending a school for retarded children. His hostility made it impossible to measure his IQ.

At 14 years of age he had some right-sided hearing loss though his tympanic membranes were normal. After this time he attended an adult clinic.

Case 3. The patient's birthweight was normal, but he failed to grow at a normal rate. At 2 years of age he developed brown spots on his body, and these slowly increased in number, size, and darkness. He was investigated at 10 years of age in the Churchill Hospital, Oxford, because he was small. No renal, bone, or absorption defect was found. His IQ was 85. His primary dentition was delayed and his secondary dentition was very carious, and for this reason his teeth were removed at 11 years of age. At 12 years of age a bilateral orchidopexy was performed. He had no symptoms referable to the cardiovascular system but had had two short periods of unconsciousness while travelling on a bus. Profuse pigmented lentiginous, 1 mm to 1 cm in size, covered his body (Macmillan (for Vickers), 1969). His height was below the 3rd centile and skeletal maturation was normal for his age. He was in sinus rhythm. The rest of the examination of the cardiovascular system was normal except for an ejection sound at the left sternal edge and an ejection systolic murmur in the pulmonary area after exercise only. Chest x-ray was normal. ECG showed left axis deviation (270°), with marked clockwise rotation with upright T waves in V1 suggesting right ventricular hypertrophy (Fig. 3). Right heart catheterization

(b)

(c)

...wave inversion in left-sided chest leads. (b) Face. (c) Trunk, front view

TABLE
Reported Cases of

Reference	This Report			Zeisler and Becker (1936)	Moynahan (1962)				Walther <i>et al.</i> (1966)			Capute (1969)
Case No.	1	2	3	4	5	6	7	8	9	10	11	12
Sex	M	M	M	F	F	F	M	M	F	M	F	F
Little (small stature)	+	—	+	+	+	+	+		+	+	+	
Lentigines	+	+	+	+	+	+	+	+	+	+	+	+
ECG	+	+	+						+	+	+	
Ocular	+	+	—	+							+	
Pulmonary stenosis, HOCM, etc.	+	+	—		+	+		+	+	+	+	+
Abnormal genitalia	+	+	—		+	+	+			+		
Retarded mentally	+	+	+		+	+	+			+		
Deaf	+	+	—									+

+ Found. — Not at present. Blank: Not tested.

showed normal pressures and saturations on pulmonary capillary wedge, but the procedure was discontinued because of transient heart block. The electroencephalogram suggested epilepsy.

Discussion

Previous reports of this syndrome are summarized in the Table. Zeisler and Becker (1936) described a case with multiple lentigines, pectus carinatum, ocular hypertelorism, and mandibular prognathism, but no cardiac defects. Moynahan (1962) reported lentigines in 4 unrelated patients, 2 females and 2 males of reduced stature and normal intelligence. Both girls had psychic infantilism, short stature, endomyocardial fibroelastosis, and delayed puberty. One girl had a single hypoplastic ovary. Both boys were short. One had 'endomyocardial elastosis (congenital mitral stenosis)', the other a normal heart. One had an ectopic right testis and hypospadias. His EEG was stated to show 'manifestations of immaturity'.

Walther, Polansky, and Grots (1966) reported multiple lentigines and cardiac abnormalities in a mother and 2 of her 3 children. The mother was below the 3rd centile for height. Her menarche had been delayed to 18 years. The EEG 'suggested right bundle-branch block and a pattern associated with infarction of the anterior third of the interventricular septum with superior displacement of the QRS loop'. Cardiac catheterization indicated mild pulmonary valvular stenosis. Her 11-year-old son was below the 3rd centile for height and weight. The ECG showed a 'superiorly oriented QRS frontal axis . . . abnormal T waves over the left precordium and incomplete right bundle branch block'. The vectorcardiogram showed the QRS loop to be placed superiorly and to the right.

Right-sided cardiac catheterization showed no abnormality. Subsequently, this child developed a grade 4 systolic murmur without change in the chest x-ray or ECG. Though he had had a reading problem, his hearing was normal. The sister of this boy was below the 25th centile for height. Her ECG showed non-specific ST to T wave changes, with a left axis deviation -50° . The QRS loop on the vectorcardiogram was posterior and superior with clockwise rotation of the sagittal plane. She had strabismus of the right eye.

Capute (1969) noted multiple lentigines and congenital deafness in a mother and daughter. Both developed a grade 2 pulmonary ejection systolic murmur. Matthews (1968) described multiple lentigines in a mother and 2 of her children by different marriages. The mother had a systolic murmur with frontal axis of -90° . Her son had mild pulmonary stenosis and her daughter by a different marriage also had a systolic murmur. The daughter's ECG showed deeply inverted T waves and depressed ST to T segments in leads V3 to V6, with a QRS axis of -20° .

Kraunz and Blackmon (1968) described a woman with diffuse lentigines in whom cardiac catheterization showed subaortic and subpulmonary stenosis. Her ECG showed left 'ventricular hypertrophy and strain, and possible right ventricular hypertrophy'. Lewis *et al.* (1958) described a Negro family in which the mother and 3 of her 5 children had pulmonary stenosis. Two of these children were deaf. In a later report on the same family (Koroxenidis *et al.*, 1966), one of 3 children born to the mother by a second marriage had retarded growth, ocular hypertelorism, and undescended testes. Lentigines were not mentioned, possibly because the patients were Negroes. Gorlin *et al.*

Little Leopard' Syndrome

Matthews (1968)			Kraunz and Blackmon (1968)		Lewis <i>et al.</i> (1958)				Gorlin <i>et al.</i> (1969)						Moynahan (1970)		Total
14	15	16	17		18	19	20	21	22	23	24	25	26	27	28	29	29
F	M	F			F	M	M	M	M	M	F	M	M	F	M	M	
+	+	+	+			+	+	+	+	+	+	+	+		+	+	19
+	+	+	+						+	+		+	+		+	+	23
									+		+	+	+	+			17
									+			+	+	+			12
+	+	+	+		+	+	+	+			+	+	+	+	+	+	24
						+	+	+	+			+	+				13
																	7
					+		+	+	+								8

(1969) have presented a full report of 6 cases containing up to 6 of the 8 criteria for this syndrome. The striking appearance of our patients makes the term 'Little Leopard' an apt and useful mnemonic for recalling the features of the condition. This is a genetic condition inherited as an autosomal dominant affecting several systems, mainly those derived from ectoderm and mesoderm. Chromosomes were normal in Case 1, the only case in which they were studied. Moynahan speculates that the gene concerned in this syndrome is one which interferes with the development of neural crest elements leading to hyperactivity of melanocytes in skin (lentiginosis) and of the β -adrenergic effectors in cardiac muscle thus accounting for the abnormal

ECG's and obstructive cardiomyopathy. That melanocytes play a part in the development of the male genital tract may account for abnormalities of the genitalia. He suggests that some disturbance of pigment metabolism in the brain, associated with dopamine and catecholamines, delays growth and sexual maturation. The prognosis is determined by the cardiac lesion. All three of our cases and most of those reported by others had a cardiomyopathy, which is usually of the obstructive type. The only sign of a cardiac abnormality in our Case 3 was left axis deviation, suggesting that all Little Leopards be seen at regular intervals by a cardiologist. He can watch for the development of cardiomyopathy and if neces-

FIG. 3.—Case 3. ECG shows left axis deviation.

sary prescribe propranolol in an attempt to prevent or defer the sudden death which may be seen in these cases (Moynahan, 1970).

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Correspondence to Dr. D. Pickering, Department of Paediatrics, The Radcliffe Infirmary, Oxford.