DE LANGE SYNDROME — A CASE REPORT

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We ought not to set them aside with idle thoughts or idle words about "curiosities" or "chances". Not one of them is without meaning; not one that might not become the beginning of excellent knowledge, if only we could answer the question — why is it rare? or being rare, why did it in this instance happen? — James Paget, 1882 *Lancet,* 2:1017.

In 1933 the Dutch paediatrician Cornelia de Lange described a new syndrome of mental retardation occurring in children with a characteristic facies (de Lange, 1933). The syndrome is rare, and just over 200 cases have been mentioned in the literature (Abraham and Russell, 1968). I report here a patient with the de Lange syndrome who also has a rare type of cyanotic congenital heart disease.

Case Report

The 5-year-old patient is the illegitimate daughter of a secundiparous epileptic and mentally retarded Maltese mother. She was born at 38 weeks after a normal pregnancy and breech extraction. The birth weight was 2580 grams (5 lbs 6 oz). There were no respiratory difficulties at birth.

At 6 weeks of age prior to her discharge from hospital weighing 3300 grams (6 lbs 14 oz), the child was found to have a loud systolic cardiac murmur. Subsequently, she failed to thrive and suffered from repeated chest infections. It soon became obvious that the child was severely mentally retarded and because of the unsatisfactory home background she was for a time placed in an institution.

She is now 5 years old, shows considerable delay in both her mental and physical development and takes only a limited interest in her surroundings. Her speech maturation is especially defective, and she cannot produce an intelligible sound. She can barely sit up unsupported and cannot eat any solids. She rarely smiles, is easily upset when handled and frequently indulges in head banging, body rocking and hair pulling.

On examination, she is an ugly-looking child with marked central cyanosis and orthopnea and shows the typical de Lange syndrome facies *(Fig. 1)*. Her weight is 8.7 Kg. (19 lbs 1 2oz), her length 82.5 cms (32.5 inches) and the chest circumference: 53.3 cms (21 inches). All these measurements lie well below the 3rd percentiles. The skin shows hypertrichosis and cutis marmorata.

Facies: She is microcephalic—head circumference: 45.7 cms (18 inches)) with a flattened skull (brachycephaly). The hair is lustreless and the occipital and frontal hair-lines are low. The bushy eyebrows meet in the midline (synophyrs), the eyelashes are long and there are bilateral medial epicanthic folds. The bridge of the nose is depressed and the nostrils anteverted. The ears are normally formed but are low-set. The chin is small (micrognathia). The large mouth shows distinctive features. There is an increase in the distance between the nostrils and the upper lip, which has only a small philtrum in the midline. The lower lip is rather prominent and the angles of the mouth curve downwards. There is a high-arched palate and dentition is faulty.

Limbs: Changes in the upper limbs

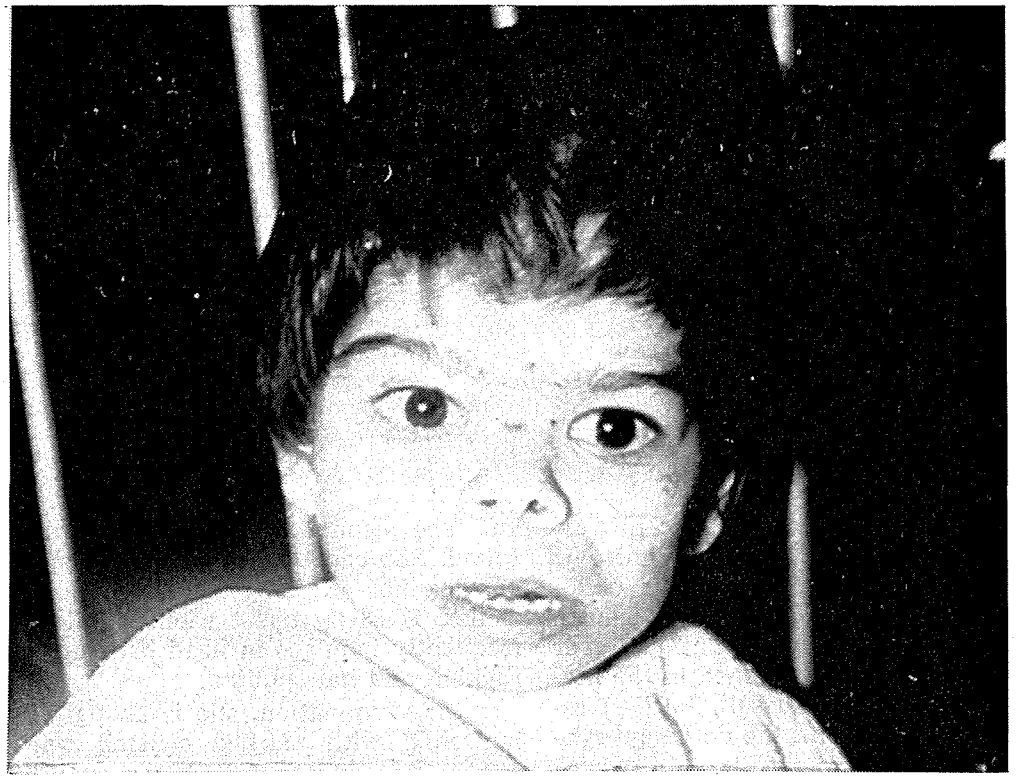

Figure 1

include limited flexion of both elbows, simple palmar creases, slightly incurved little fingers (clinodactyly) and gross clubbing. The thumbs are proximally placed and broad. The legs are thin, the right shorter than the left. There is bilateral genu recurvatum, that on the right being fixed due to contracture of the vastus intermedius. The feet show toe clubbing, minimal overlap of the 4th over the 5th toes and long big toes. The heels are prominent.

Chest and Abdomen: There is dorsal kyphoscoliosis with a slight lateral curve, convex to the left. The chest is barrel-shaped with a marked left chest bulge and a short sternum. The apex beat is in the 4th left intercostal space on the anterior axillary line. There is no right ventricular heave. A grade 3/6 long ejection murmur is heard best at the upper left sternal border. The second sound is single and not accentuated. The lungs are clear to auscultation. The percussion note is tympanitic in the right hypochondrium and the liver edge is palpable on the left. The spleen and kidneys are not palpable.

Investigations carried out are as follows: Hb. 15.7Gm%; P.C.V. 60%; W.B.Cs 7,600/cu.mm Neutrophils: 36%; Lymphocytes: 44%; Monocytes: 17%; Eosinophils: 2%. The peripheral smear shows moderate anisocytosis, poikilocytosis and anisochromia. Occasional target cells are present. No stippled erythrocytes, Howell-Jolly bodies, Heinz bodies or nucleated R.B.Cs are seen.

The E.C.G. shows the Wolff-Parkinson-White syndrome. There are also upright P waves in leadsI, aVL and left ventricular chest lead and bi-ventriculra hypertrophy more right then left.

X-Ray Chest and Upper Abdomen *(Fig. 2)* shows gross cardiomegaly with a ball-shaped heart, with the cardiac apex pointing to the left. The lung fields are cligaemic. The liver shadow is present on the left side and the stomach and intes-

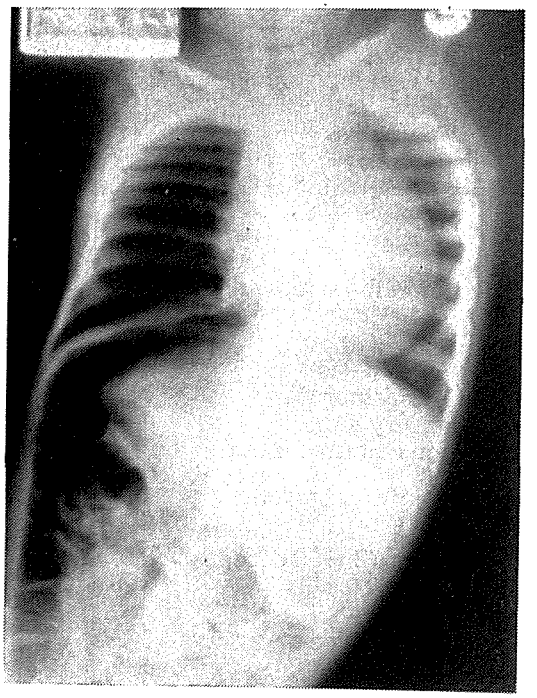

Figure 2

tinal gas shadows are mainly on the right side. No spleen shadow is visible. X-ray hands and forearms shows delayed bone age (corresponding to that of a $2\frac{1}{2}$-year old), rather small but thick 1st metacarpals and small middle phalanges of the fifth fingers. The head of the radius appears normal but the glenoid fossa is rather shallow on both sides.

Comments

This patient shows most of the classical morphological characteristics of the Cornelia de Lange syndrome. The table compares the clinical features of this case with those of the 9 cases described by Abraham and Russell (1968).

The aetiology is still uncertain and the vast majority of cases are sporadic. Various chromosomal anomalies have been observed in a few of the cases who have had chromosome analysis but the significance of these findings is still doubtful.

Diagnosis of the condition rests chiefly in recognising the combination of severe mental and physical retardation and the peculiar facies. Of the facial features, the two most important are the bushy eyebrows meeting in the mid-line and the curved, thin upper lip with absent philtrum and sometimes with a corresponding notch in the lower lip. Certain X-ray abnormalities are also characteristic, notably the short thick 1st metacarpals and the small, sometimes rudimentary 2nd phalanges of the little fingers. The heads of the radii are also not uncommonly malformed. Bone age is delayed in most cases.

Studies in dermal ridge patterns of the hands (dermatoglyphs) have shown mainly an increased number of radial loops in the finger tips of the middle three fingers and commonly, a loop from the c triradius into the third interdigital space of the palm (Smith 1966).

Congenital heart disease is not uncommon in these patients. With situs inversus of the abdominal viscera, there is usually dextrocardia. Rarely, as in the case here described, situs inversus is associated with a normally-placed heart — a condition known as "situs inversus with laevocardia". Campbell and Forgacs (1953) could only discover 14 cases among 1130 patients with congenital heart disease, an incidence of about 1%.

In the majority, the heart chambers are normally placed but in one-third of cases inversion of the atria is also present. This may or may not be accompanied by corresponding inversion of the ventricles. Irrespective of whether chamber inversion is present or not, multiple and extremely complex cardiac lesions, usually of the cyanotic group, generally accompany this anomaly. These include: 1) abnormal systemic vein connections; 2) anomalies of the great vessels and septal defects; and 3) right- sided aortic arch (Gasul *et al.* 1966).

Two other interesting defects often coexist. Firstly, there is in the majority of cases abnormal lobulation of the lungs, which are symmetrical and have three lobes each. Secondly, congenital absence or agenesis of the spleen (asplenia) is common. This is usually associated with repeated severe chest infections and the presence of numerous Howell-Jolly bodies (nuclear remnants) and Heinz bodies

		Present case			Present case
FACIES			HANDS		
Synophrys	9/9	+	Proximal thumb	8/9	+
Long upper lip	9/9	+	Fifth clinodactyly	8/9	+
Anteverted nostrils	8/9	+	Simian crease/s	9/9	+
Depressed nose bridge	6/9	+	Tapering fingers	4/9	−
Hypertelorism	3/9	−	Finger clubbing	2/9	+
Anti-mongoloid slant	5/9	−			
Epicanthic folds	2/9	+	ARMS		
Eccentric pupils	4/9	−	Limited elbow movements	3/9	+
Micrognathia	7/9	+			
Prominenet symphysis mentis	4/9	−	SKIN		
High arched palate	3/9	+	Hypertrichosis	8/9	+
Long eyelashes	O	+	Cutis marmorata	7/9	+
Low-set ears	O	+	Rough dry skin	4/9	−
			Ginger coloured scalp hair	2/9	−
SKULL					
Microcephaly	9/9	+	FEET		
Brachycephaly	5/9	+	Webbing (2 + 3) toes	8/9	−
X-RAY CHANGES			OTHERS		
			Growling voice	6/9	+
Short thick 1st metacarpal	9/9	+	Heart murmur	4/9	+
			Birth weight < 6 lb.	9/9	+
Small 2nd phalanges 5th fingers	9/9	+	Failure to thrive	9/9	+
			Genu recurvatum	O	+
Malformed dislocated radial heads	2/9	−	Big first toes	0	+

Features of present case compared with those reported by Abraham and Russel (1968).
+ = present; − = not present; O = not mentioned.

(precipitated haemoglobin) in the R.B.Cs of the peripheral smear. Normally, the spleen is able to remove these bodies from within the red cells without destroying them (Crosby 1959). Similar changes to the above occur in the peripheral blood of patients who have undergone splenectomy.

Laevocardia with situs inversus is often missed during physical examination because when the heart is normally on the left, one tends to perform a cursory examination of the abdomen without specifically looking for the relative positions of the liver and of the stomach. It is only recognised retrospectively after X-Ray examination of the chest and upper abdomen.

In the absence of selective angiocardiography in our patient it is not possible to delineate the exact nature of the complex cardiac anomaly.

Acknowledgement

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References

Abraham, J.M., and Russell, A., (1968) — Acta Paediat. Scand. *57*:339.
Campbell, M. and Forgacs, P. (1953) — Brit. Heart J. *15*:401.
Crosby, W.H. (1959) — Blood *14*:399.
De Lange, C. (1933) — Arch. Med. Enfant *36*:713.
Gasul, B.M., Arcilla, R.A., and Lev, M. (1966) — Heart Disease in Children, Philadelphia J.B. Lippincott Co., P. 1071.
Smith, G.F. (1966) — J. Ment Def. Res. *10*:241.