THE LEOPARD (MULTIPLE LENTIGINES) SYNDROME: A CASE REPORT

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SUMMARY

A case of the leopard (multiple lentigines) syndrome is described. To our knowledge this is the first documented case of this rare but interesting syndrome to be reported in this country.

INTRODUCTION

Lentigines are small brown macules in the skin characterised histopathologically by an increased number of melanocytes at the dermo-epidermal junction. Profuse lentigines, first described in the literature as 'lentiginosis profusa' was thought to be a dermatologic oddity. Later reports appeared of an association with cardiac abnormalities and sexual infantilism. [1] Based on further observations, Gorlin and Anderson [2] in 1969 tied together a melange of manifestations that are associated with profuse lentigines and establised the LEOPARD syndrome, named acrostically from the main findings as follows: L - lentigines, E - electrocardiographic conduction abnormalities (usually bundle branch blocks), O - ocular hypertelorism, P - pulmonary stenosis (other cardiac abnormalities like aortic stenosis and hypertrophic cardiomyopathy have also been reported, [3,5] A - abnormalities of genitalia (usually hypospadias and cryptorchidism), R - retardation of growth, D - Deafness (sensori-neural).

Since the description by Gorlin and Anderson several reports of the syndrome have appeared in the literature. Some authors prefer the term 'multiple lentigines syndrome' to the 'leopard syndrome'. [4]

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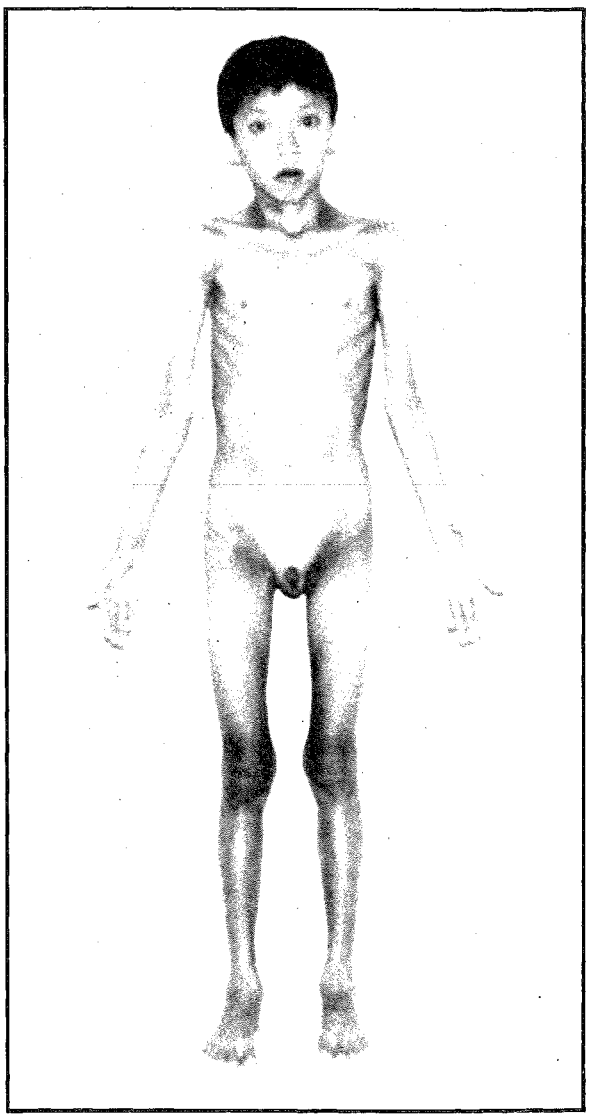

Fig. 1 Full frontal view of patient. Note mild ocular hypertelorism, infantile genitalia, absence of pubic hair and lack of muscle bulk.

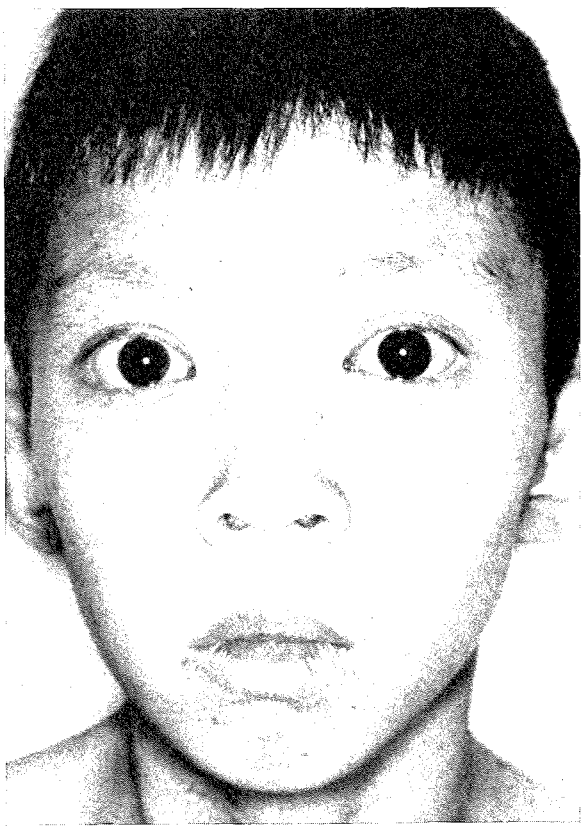

Fig. 2 Face showing a large number of lentigines.

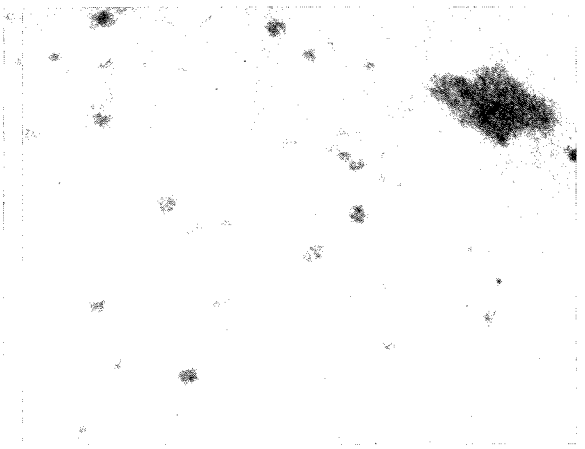

Fig. 3 Close-up of lentigines and a cafe-au-lait spot.

CASE REPORT

A 17 year old Chinese male presented with exertional dyspnoea for 2 years.

The patient had been a deaf-mute since birth. The mother did not have any rash or fever suggestive of rubella during the pregnancy. The boy developed normally till 7 years of age. Then growth ceased. At this age the patient developed some lentigines which spread and became profuse. At the age of 15 he noticed exertional dyspnoea associated with swelling of the abdomen and intermittent edema of the ankles. He had been on digoxin and lasix since then.

Despite the deaf-mutism the patient had managed to learn to read and write as well as understand sign language.

The parents were non-consanguinous. There were 3 siblings who were all normal.

Examination at admission revealed a thin boy (Fig. 1) who was short for his age - the height was only 1.36 m and his younger siblings were taller than him. He was underweight as well (24 kg). He appeared intelligent and was able to communicate effectively by writing. There was mild jaundice but no edema. A large number of lentigines 2 - 5 mm in size were present on the face and upper trunk together with 2 larger 'cafe-au-lait' spots (Figs. 2 and 3). There was mild ocular hypertelorism. The jugular venous pressure was elevated to the angle of the jaw. There was a prominent presternal bulge. Marked clinical right ventricular hypertrophy was evident and a long systolic murmur (grade 5/6) was heard over the pulmonary area. The muscles were generally lacking in bulk and winging of both scapulae was observed. There was no axillary or pubic hair. The penis measured only 3 cm and the testes were unusually small (2 cm x 1.3 cm) with the right testis situated at the external inguinal ring. The lungs were clear. There was moderate hepatomegaly and mild splenomegaly. No ascites was detected. The visual fields were normal.

On investigation the haemoglobulin was 12.7 g/dl. Blood urea, creatinine, electrolytes, calcium, phosphate and urinalysis were normal. The serum bilirubin was slightly elevated (42 mmol/1) but the transaminases and serum proteins were normal. Urine hydroxyindoleacetic acid level was not increased. Blood testosterone level was 0.9 mmol/1 (normal 11.6 - 36.6 mmol/1). The bone age on X-ray was only 7 years.

Skin biopsy of a lentigo showed increased melanocytes in the basal layer typical of the condition (Fig. 4). Audiometry demonstrated severe hearing loss of the sensori-neural type in both ears.

Chest X-ray showed marked cardiomegaly.

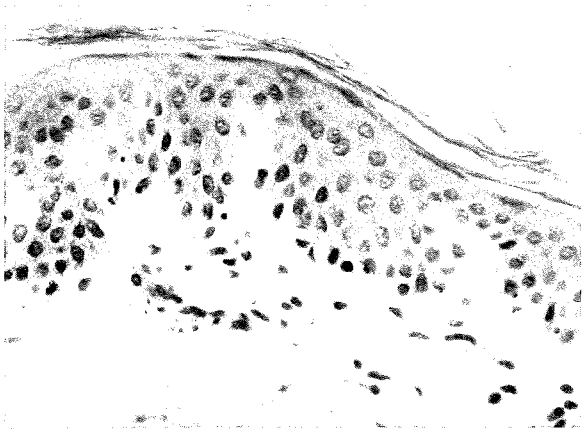

Fig. 4 Photomicrograph of lentigo showing increased number of melanocytes (visible as clear cells with dark-staining nuclei) in the basal cell layer and increased melanin deposition in the epidermis (Hematoxylin-eosin x 250).

Electrocardiogram showed right ventricular hypertrophy with sinus rhythm and a first degree heart block. The QRS axis was +160°, which indicated a left posterior hemiblock in addition. Cardiac catherisation revealed obvious right ventricular hypertension and the angiogram of the right ventricle (Fig. 5) showed pulmonary valvular stenosis and a huge dilated right ventricle.

The liver scan showed 'non-specific hepatosplenomegaly' with no visible focal defects. We did not investigate the hepatosplenomegaly further and attributed this and the mild jaundice to prolonged and severe right heart failure. The kidneys were normal on ultrasound. Electroencephalogram (EEG) was normal and so was the peripheral nerve conduction time. The electromyogram (EMG) of muscles related to the winged scapulae was normal and the creatinine phosphokinase (CPK) level was also not raised.

DISCUSSION

Our patient had all the features of the leopard syndrome.

Apart from the 7 main features listed under the acronym 'leopard', other features reported to occur with this syndrome include pectus carinatum or excavatum, dorsal kyphosis and winging of the scapula. [3] Our patient did have bilateral winging of the scapula as an added feature. The previous reports have not provided any explanation for this finding. We wondered if it could be due to an associated myopathic process like muscular

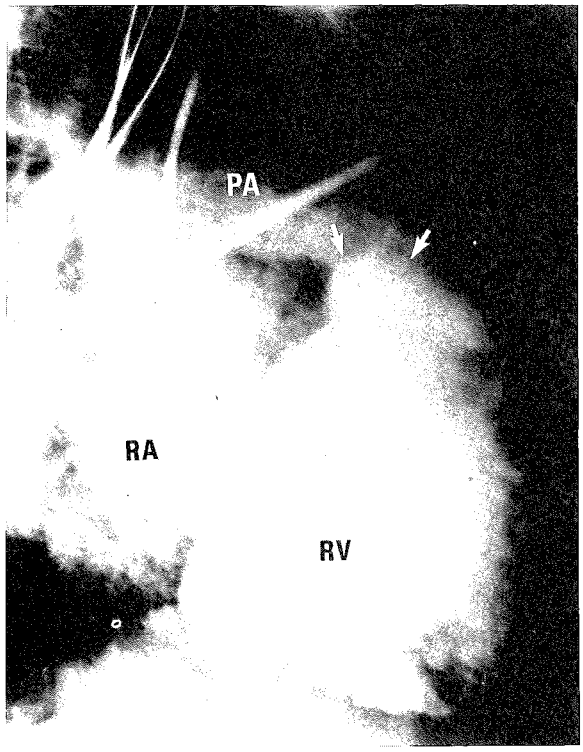

Fig. 5 Angiogram showing a grossly dilated right ventricle (RV) and stenosed pulmonary valve (arrowed) with post-stenotic dilatation of pulmonary artery (PA). RA - right atrium.

dystrophy. However the normal EMG and normal CPK level make this an unlikely reason. There is a single report of an association with unilateral renal agenesis [7] but ultrasound in our patient did not show such a feature.

Classically the leopard syndrome is a familial condition and studies of several pedigrees have indicated an autosomal dominant inheritance with high penetrance and variable expressivity. [3] The latter behaviour of the gene accounts for the rather protean presentation of the syndrome seen clinically. Even in the same family some affected individuals may show only some of the features of the syndrome while others may have all the features.

Our patient appears to be a sporadic case. We had the opportunity of examining the parents and the 3 siblings (1 male and 2 females) and none of them had any features of the syndrome. This is not an isolated finding. There are other well documented cases in the literature that are sporadic. [3,4,7] Perhaps these cases represent new

mutations.

An embryologic theory has been proposed to explain the combination of the various features of this syndrome. It is known that melanocytes are derived in the embryo from the neuroectoderm. They are responsible in part for formation of the inner ear. A genetic abnormality affecting the neuroectoderm could hence account for both lentiginosis and deafness. [4] That melanocytes play a part in the development of the male genital tract may account for abnormalities of the genitalia. [6] The presence of abnormalities in the heart and skeletal system, which are of mesodermal origin, is more difficult to account for. However, a possible explanation lies in the pleiotropic nature of genes. [4] Most genes are thought to be responsible for the production of a single protein with a specific enzymatic or regulatory function. A mutant gene produces a quantitative or qualitative deficiency of this protein and every cell or cell function dependent in any way on the proper functioning of this one protein could be affected to some degree. This biochemical interaction between one abnormal cell population with cells from other tissues may be responsible for abnormalities in another system. [4]

Nordlund *et al* [4] in support of the theory of a primary neuroectodermal defect have reported widespread neurological abnomalities as evidence by delayed peripheral nerve conduction and diffuse EEG abnormalities in a patient with the multiple lentigines syndrome. We were not able to confirm his findings. The EEG and peripheral nerve conduction in our patient were both normal.

Awareness of the leopard syndrome is important because the manifestations are variable and some patients may have only lentiginosis and cardiac abnormalities. In such cases the lentigines may precede the development of cardiac abnormalities. [5,6] Valvular cardiac lesions detected early may be amenable to surgery while early hypertrophic cardiomyopathy may respond to drugs like B-blockers.

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