

LEOPARD syndrome. The first case reported in Saudi Arabia.

Shelleh H.H., Saleh A.M., Ibrahim M.S., Sumangala B., Dawood S.
Najran General Hospital, King Khalid Hospital, Najran, Saudi Arabia

Summary

We report on a 3-year-old Saudi boy who demonstrated lentigines, hypertrophic cardiomyopathy, ocular hypertelorism and deafness, thus fitting the diagnosis of LEOPARD syndrome or Multiple Lentigines Syndrome. It was a sporadic case. The patient manifested almost all the clinical features included in the acrostic LEOPARD except A "abnormality of genitalia" which might appear later, and P "pulmonary stenosis" which was replaced by hypertrophic cardiomyopathy. Lentigines were the clue sign leading to the diagnosis. The child was missed for follow up, to expire suddenly at the age of 8 years as we knew later. This case from the south of Saudi Arabia documents the presence of LEOPARD syndrome in this region, and is thought to be the first Saudi LEOPARD reported. Patients with early onset LEOPARD syndrome have a poor prognosis owing to the rapid progression of the cardiac lesion, thus they should be followed up carefully to avoid the fatal complications. We would like to remind that lentigines should not be clinically neglected, because they may serve as a clue of catastrophic syndromes.

Key words

LEOPARD syndrome, hypertrophic cardiomyopathy.

The LEOPARD syndrome (LS) is a rare cardio-cutaneous disorder transmitted by an autosomal dominant trait and with variable expression. Each letter of the acrostic stands for a definite representative feature of it, though this representation became controversial for some of them, particularly **L** for lentigines, **E** for ECG abnormality, **O** for ocular hypertelorism, **P** for pulmonary stenosis, **A** for abnormality of genitalia, **R** for retarded growth and **D** for deafness. This smart acronym was first coined by Gorlin in 1969 (6). Since then, case reports of LS have been issued from diverse countries with worldwide distribution. However, it was not reported before from Saudi Arabia.

Case report

A three-year-old Saudi boy was referred to skin outpatient division for asymptomatic black

spots on the skin. The lesions were present at birth, and went on increasing gradually. With the exception of deafness and delayed mile stones which the parents noticed, there was no personal or family history worthy of mention.

On clinical examination, the child was not reactive to sound, dull faced and the upper part of the head was relatively broadened resulting a triangular shaped face. The skin showed numerous deeply pigmented uniform macules (Fig. 1), which were flat and round shaped, small in size, less than 5 mm in diameter. They were scattered all over the skin including axillae, with predominance on the face and trunk, but the oral mucosa was spared. Few café-au-lait macules could be seen on the trunk.

Deafness was confirmed by the visual response audiometric assay and proved to be of the sensorineural type. The eyes were intact but the interpupillary distance was increased, measuring 50 mm in such an early age.



Fig. 1

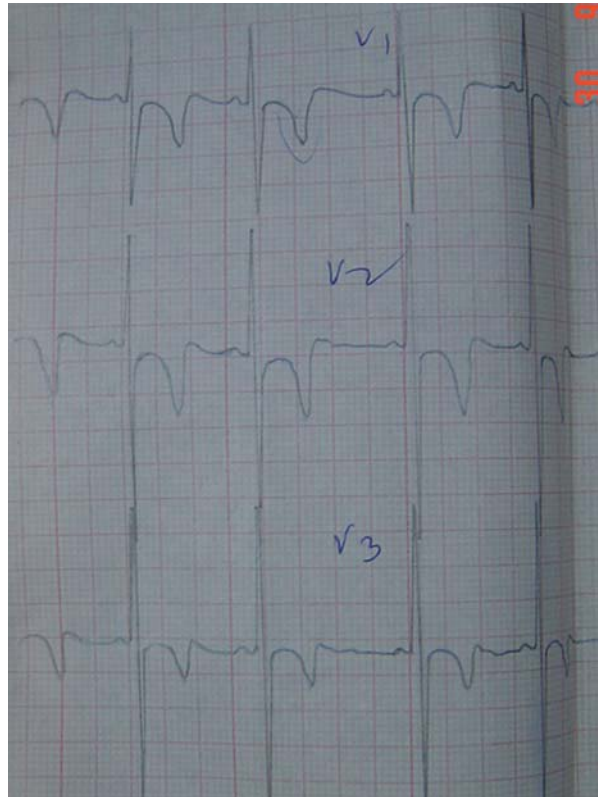


Fig. 2

Fig. 1, 2, 3, 4: LEOPARD syndrome. On the face lentigo and ocular-hypertelorism (Fig. 1). ECG (Fig. 2) shows the electrocardiographic alterations. Chest x-ray (Fig. 3) shows cardiomegaly, sign of congenital heart disease. Echocardiogram (Fig. 4) shows obstructive hypertrophic cardiomyopathy.



Fig. 3

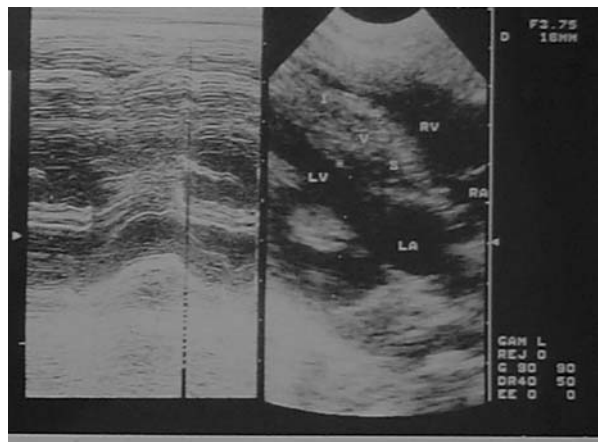


Fig. 4

The heart examination revealed parasternal heave with palpable systolic thrill over precordium, laterally displaced apical impulse and a harsh systolic murmur of grade IV intensity appreciated all over, specially along the left sternal border. The rest of the clinical examination was unremarkable. Routine blood tests were within normal limits.

Chest X-ray (Fig. 3) showed cardiomegaly, which was likely indicative of congenital heart disease. Electrocardiography (Fig. 2) showed right axis deviation, right ventricular predominance, mean QRS + 150, Q wave seen in V5-V6, inverted T wave and depressed S-T segment on V1-V3 leads. Echo-cardiography (Fig. 4) showed marked hypertrophy of the left ventricle and papillary muscles with obliteration of left ventricular cavity. Interventricular septum was markedly hypertrophic and partially obstructing the left ventricle outflow tract. The mitral valve displayed systolic anterior motion, but the pulmonary valve was quite normal. The left atrium was dilated. The overall echocardiography report confirmed the existence of obstructive hypertrophic cardiomyopathy (HCMP) with asymmetrical septal hypertrophy. Table 1 shows a summary of the clinical data as compared with the complete syndrome.

Discussion

It is intriguing to note that there are three "leopards" which can be traced in dermatological literature, all of them rare, as follows: "the leopard skin" which designates depigmented lesions merged with normal skin on the chins

within the context of onchocerciasis, "the leopard vitiligo" which described anecdotal special-spotty- form of vitiligo on the legs of 2 Indian girls, and "the LEOPARD syndrome" (LS) which represents an acrostic for the multiple lentiginos syndrome (2), the subject of this report. However, there are also "the little leopards" which designate incomplete forms of LS, or with mental retardation (11).

The diagnosis of LS relies solely on the clinical findings. As this child has five of the seven signs represented in the acrostic LEOPARD, the diagnosis of LS is quite fair. This makes him clinically an "ideal leopard" amongst the widespread little/incomplete ones in literature (1, 17). However, it is too early to exclude A; "abnormality of genitalia" as he is three years old yet. In the LEOPARD syndrome, each letter represents a feature in it successively (6). Nevertheless, not all these well arranged acrostic features represent the most prevalent ones as proved later on. Starting with lentiginos, they are the most constant and characteristic feature of LS, found in 100% of the patients (4). They are histologically of lentigo simplex type, scattered all over the skin but avoiding the oral cavity. They may be associated with café-au-lait spots, as in our patient, and these may fulfill in size and number Crowe's criteria for neurofibromatosis and cause diagnostic confusion (10).

With regard to electrocardiography, axis deviations and left anterior hemiblock, which were found in this patient, were reported before in LS. Some Authors regard the conduction defects as the most frequent cardiac abnormalities in LS (14). The cardiac lesion is reported in 80-90% of LS cases (4, 18). However, there is

TABLE 1

	L	E	O	P	A	R	D
LEOPARD	Lentigo	ECG defects	Ocular hypertylor.	Pulmonary stenosis	Abnormal genitalia	Retarded growth	Deafness
propositus	+	+	+	HCMP	?	+	+

controversy about the most common anatomical cardiac lesion in LS, whether pulmonary stenosis (PS), as first reported by Gorlin (2, 4, 6, 7, 18), or HCMP as frequently reported later on (8, 12). On a fast review of literature, the eye will not miss how common HCMP is. Our patient with HCMP and intact pulmonary valve supports this view.

Skeletal anomalies are frequently reported in LS. These may contain a list of bony defects including ocular hypertelorism, which was found in 40-50% of cases (4). The bony defects usually result in triangular face, as in this boy.

The urogenital defects are reported in 29% of LEOPARD patients (4) and include hypospadias, cryptorchidism, infantilism, gonadal hypoplasia, delayed puberty, etc.. There are no obvious urogenital defects in our patient, but they cannot be ruled out due to the age of our case.

It is worth of mention that clinical diagnostic criteria has been suggested based on the physical evaluation of dysmorphisms and malformations outlined by Voron et Al. (18). LS has a worldwide distribution; it does not respect racial or geographic lines. This case report documents the presence of LS in Saudi Arabia, and adds a new geography to the its global incidence.

Review of literature shows that most of the LS cases are sporadic as new mutations. This is

probably due to the fact that LS, with the diverse urogenital defects, affects the fertility status and reproduction potential of LS patients, but, once the fertility is spared, the disease follows a familial form with autosomal dominant trait. The etiology of LS is unknown, but it is thought to be a type of ectodermopathy with autosomal dominant mannerism. Mutational disruptions affecting melanocytes may also affect all the neural crest derived cells which contribute to the formation of bones, muscles, leptomeninges, soft tissue of the face and the conductive system of the heart, probably due to the parallel fetal development of adjuvant located tissues (9). In a recent study of 24 index patients of LS, 21 (88%) harbored PTPN11 gene mutations. Seven of them were identified, and all were in exons 7, 12, and 13 (13).

Our message is to remind that early onset LS children have usually poor prognosis, thus, they should be followed up carefully from the cardiac point of view to avoid the rapid catastrophic progression of the disease, as occurred with this child.

Secondly physicians should remember that black spots like lentigo simplex should not be overlooked in clinical examination because they may be the clue of different potentially fatal syndromes.

Address to:
Dr. Hamdi H. Shelleh
PO Box: 52
Najran, Saudi Arabia
e-mail: hhs_s2000@hotmail.com

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