Syndrome of the month

Multiple lentigines syndrome (LEOPARD syndrome or progressive cardiomyopathic lentiginosis)

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The multiple lentigines syndrome is an autosomal dominant condition which has many similarities to Noonan syndrome,¹ except in the most striking feature from which its name is derived. The less neutral but very apt mnemonic, LEOPARD syndrome, was first used by Gorlin *et al*² to whom the major debt in the definition of this syndrome lies,³ that is, **L**entigines, **E**CG abnormalities, **O**cular hypertelorism/**O**bststructive cardiomyopathy, **P**ulmonary valve stenosis, **A**bnormalities of genitalia in males, **R**etardation of growth, and **D**eafness. Not previously included in the mnemonic is cardiomyopathy which is an important feature because it is associated with significant mortality.

(J Med Genet 1997;34:582-586)

Keywords: cardiomyopathy; deafness; lentigines; pulmonary stenosis

The first documented case was probably that described in 1936 by Zeisler and Becker,⁴ who presented a 24 year old woman with lentiginosis and pectus carinatum to the American Dermatology Association. Photographs show hypertelorism and ptosis. In 1966 Walther *et al*⁵ described a family with ECG abnormalities, systolic murmurs, and lentiginosis. In 1968 Matthews⁶ described lentigo with electrocardiographic changes. In 1972, after the 1969 publication of Gorlin *et al*² established the condition as a distinct entity, Polani and Moynahan⁷⁻⁹ re-reported a sibship previously reported by themselves in an article involving eight patients in a total of six families. In 1975, Voron *et al*¹⁰ presented a new case and reviewed the subject, pointing out the highly variable manifestations and suggesting criteria for the diagnosis. Many others have contributed to the more than 80 cases reported to date.¹¹⁻¹⁵

Clinical presentation

LENTIGINES AND OTHER PIGMENTARY CHANGES
Classically, thousands of lentigines appear in childhood and increase in number until puberty.⁷ They are flat, dark brown to black in colour, and 1 to 2 millimetres in size, although they can be larger and are then described as café noir patches (fig 1).² These may be

Figure 1 Typical multiple lentigines in an adult with café noir patches.

congenital.⁵⁻⁷ They are present on the palms, soles, face, scalp, and external genitalia,¹⁶ but less so in these areas than the rest of the body. The irides may be involved but not the fundi.⁷ The mucosae are spared. The colour and density of the lentigines are not related to sun exposure, which differentiates them from freckles. Some patients lack lentigines¹⁷⁻¹⁸ and this makes the diagnosis difficult in the absence of deafness or a family history of lentigines. Additional cases presented by Gorlin *et al*¹⁸ in 1971 included a mother and son who both lacked lentigines but whose other features included sensorineural deafness, ocular hypertelorism, pulmonary stenosis, and (in the son) undescended testes. They also presented a cousin of a previously reported family who had dysplastic pulmonary valve stenosis and the typical ECG changes, but in contrast to the proband lacked lentigines.¹⁸

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On histological examination of the lentigines there is pigment accumulation in the dermis as well as the deeper layers of epidermis. There is an increase in melanocytic density owing to corrugation of the dermoepidermal junction. There are no naevus cells and the rete ridges are prominent.^{10 11 19 20}

Café au lait patches as well as axillary freckling have been described.^{10 21} Localised hypopigmentation (in one case in places where previous lentigines existed) is also a known feature.^{22 23}

CARDIOVASCULAR ABNORMALITIES

The frontal plane QRS axis is rotated anti-clockwise so as to be superiorly orientated and generally lies between -60° and -120° . This feature is not present in all cases and conversely may be the only cardiovascular feature, and is a useful diagnostic clue.^{5 10 24}

Valvular pulmonary stenosis is the commonest anomaly, occurring in 40% of reported cases.²⁵ It is usually mild. It occurs either as typical valvular pulmonary stenosis¹⁸ or more commonly as a dysplastic pulmonary valve.^{2 13} In a dysplastic pulmonary valve, three leaflets are present with no fusion of commissures, but the leaflets are poorly mobile owing to dysplastic myxomatous deposits.¹³ No ejection click is present in this instance. Infundibular and supra-valvular pulmonary stenosis have also been described.²⁵

Hypertrophic obstructive cardiomyopathy (HOCM) is a major concern in these patients and echocardiography to exclude this should be offered to all patients regardless of symptoms. It may be progressive and commonly involves the intraventricular septum.¹¹ In 30%, right ventricular outflow tract obstruction is also present. Muscular subaortic stenosis may or may not be part of HOCM.¹⁰ Heart block, bundle branch block, hemiblock, atrial septal defect, arrhythmias, and endocardial fibroelastosis have all been described in multiple lentigines syndrome.^{7 10-12 24 26}

DYSMORPHIC FEATURES

The principal facial features include ocular hypertelorism, broad, flat nose, low set, posteriorly rotated ears, and ptosis.^{2 10 25} These patients often have a short neck which may be webbed. Pectus excavatum and carinatum are common and 10% of patients have a scoliosis.^{10 27} A prognathic mandible is characteristic.² Joint hypermobility is an occasional feature, as is winging of the scapulae. These patients are usually growth retarded, their adult height being below the 25th centile, despite having normal or above average birth weights.^{10 25 28}

UROGENITAL ABNORMALITIES

A few isolated renal anomalies have been described.^{10 29} Genital hypoplasia in males, including a small penis and small, often undescended testicles, are the commonest association.¹⁰ Hypospadias, delayed puberty, absence or hypoplasia of an ovary, and late menarche are also listed.^{7 10 18} In the reported pedigrees, the affected parent is more often the

mother, suggesting that the affected male population may have diminished fertility. Many affected fathers have however been reported, thus ruling out an imprinted gene.

DEAFNESS

This is the rarest of the mnemonic features, occurring in 15-25% of reported cases.^{2 10 22 25 30} Deafness is sensorineural in nature, may be unilateral, but can be profound. Most cases have deafness diagnosed in childhood, but some are reported to have developed this in adult life.

OTHER FEATURES

Mild learning difficulty occurred in 23 of the 80 cases reviewed by Voron *et al.*¹⁰ Oculomotor defects were present in 16/80 and EEG abnormalities in 11/80 patients in this series.

Genetics

This condition is clearly autosomal dominant in its inheritance. Penetrance is high but may be incomplete. One of the additional cases presented by Gorlin *et al.*¹⁸ in 1971 was the cousin of the proband in an earlier report. His mother (aunt and sister to affected members) was of normal stature and cardiovascular status. No other features are mentioned in the report.

Expressivity is highly variable. Many of the families reported are discordant, particularly for the cardiac manifestations.

Case reports (table 1)

Case 1 presented with HOCM following the discovery of a murmur in infancy. Long term propranolol was prescribed and apart from the development of mild right ventricular outflow tract obstruction he has remained haemodynamically stable. The pulmonary valve was normal on echocardiography. At the age of 2 years he developed dark lentigines diffusely over his whole body, including his scalp, palms, and soles. Relative sparing of his back was noted. There was no involvement of fundi or mucous membranes. The anterior fontanelle closed late (at 2 years of age). He had severe unilateral right nerve deafness with normal hearing on the left. When last reviewed at 9 years, he was noted to have mandibular prognathism, mild ptosis, posteriorly rotated ears, anteverted nares, mild joint hypermobility, winged scapulae, and hypertelorism with both the inner and outer canthal distances being on the 90th centile. He also had pectus excavatum (fig 2A).

His parents had a previous child who died at birth. The cause of death was thought to have been cardiac in origin but necropsy was not performed and there was no further information. There was no family history of lentigines but his father's height was on the 3rd centile and he had downward slanting, wide set eyes with mild ptosis. He had a triangular face and a small jaw and he too had a sternal depression. He had a normal echocardiogram.

FAMILY K

Case 2 was noted to be dysmorphic in infancy. He had a large anterior fontanelle, hyperte-

Table 1 Case report features

	Case 1	Case 2	Case 3	Case 4	Case 5
Lentigines	+	+	+	+	+
OFC, centile	85-95	90	> 90	Large	50-75
Hypertelorism, centile	90	> 95	> 95	+	+
Ptosis	+	-	-	?	+
Posteriorly rotated ears	++	+	+	+	++
Superior ECG axis	+ (-90°)	+ (-130°)	+ (-105°)	+ (-70°)	+ (-55°)
Other ECG anomalies	-	+	+	+	-
Cardiac symptoms	+	-	-	+	-
Hypertrophy - septal	+	+	+	+	-
Right ventricle	+	-	-	+	-
Left ventricle	+	-	-	+	-
RVOT obstruction	+	-	-	+	-
LVOT obstruction	+	-	+	+	-
Pulmonary stenosis	-	-	-	-	-
Genitourinary features	Normal	Normal	Normal	*	Normal
Birth weight (g)	3900	2980	3440	4000	?
Latest height, centile	25-50	< 5	5-10	< 5	< 5
Deafness	Left sided only	Mild, conduction	-	Unilateral, congenital	At 59 years
Sternal abnormalities	+	+	+	-	?

+ = feature present, - = feature absent, ? = feature not ascertained, * = unilateral undescended testis, OFC = occipitofrontal circumference, RVOT = right ventricular outflow tract, LVOT = left ventricular outflow tract.

Figure 2 (A) The face of case 1 aged 9 years showing hypertelorism and lentigines. (B) Case 2 in infancy showing the typical facies. Lentigines became manifest later. (C, D) Case 3 in adulthood. Note the hypertelorism, multiple lentigines, and low set, posteriorly rotated ears.

lorism, posteriorly rotated ears, and a low posterior hairline (fig 2B). In addition he had divarication of the rectus abdominus, an umbilical hernia, an ejection systolic murmur, bilateral simian creases, short fingers, and limitation of thumb extension. At birth a 1 cm café au lait patch was present on the knee but there were no lentigines. His length was 51 cm (on the 50th centile). He had mild feeding problems. At 9 months of age he was shown to have a floppy mitral valve and thickening of the interventricular septum with bulging into the left ventricular outflow tract on echocardiography. His development was delayed; he sat at 1 year, walked at 2 years, and had speech delay. Unilateral conduction deafness was diagnosed.

By 2 years, over 10 lentigines were present on the trunk but also on the face and hands, including the volar surfaces. At the time of writing he attended a school for children with moderate learning difficulties. His height at 2 years was below the 3rd centile and remained below the 3rd centile at 6 years.

Case 3, the father of case 2, was reported to have had a few lentigines at birth with many more appearing later. On examination as an adult, he had hypertelorism, ptosis, posteriorly rotated ears, and a low hairline. In addition to the ECG findings he had mild interventricular septal hypertrophy and a floppy mitral valve (fig 2C, D).

Case 4, the brother of case 3, was one of the original cases reported by Moynahan and Polani⁷ in 1972.

Case 5, the mother of case 3, had multiple lentigines as well as two café au lait patches. The lentigines developed when she was 4 years old. She had hypertelorism, posteriorly rotated ears, anteverted nares, and short palpebral fissures. She had no documented cardiac problems when she was investigated aged 41 years. A systolic mitral murmur was noted in old age. She was treated for hypothyroidism from the age of 41 years and she developed cataracts aged 66 years. Aged 59 years she had a 50-70 dB hearing loss recorded in both ears.

Diagnosis

Diagnostic criteria were proposed by Voron *et al*¹⁰ in 1976, which included lentigines plus two other recognised features or a first degree relative with lentigines plus three other features in the patient. This still seems reasonable pending clarification of the genetic defect.

Differential diagnosis (table 2)

NOONAN SYNDROME
The presence of lentigines and deafness in LEOPARD syndrome are the only distinguishing features between this and Noonan syndrome.¹ The cardiovascular, growth, and dysmorphic findings are identical.¹ Cases of lentiginosis sine lentigines are well described in families with LEOPARD syndrome¹⁷ and such patients would be indistinguishable from Noonan syndrome in the absence of a family history. It is speculative that the two conditions may be allelic.¹

Table 2 Differential diagnosis

	Leopard	Noonan	NF1	Pj	NAME
Skin lentigines/freckling	+ (93%)	–	+	+	+
Mucosal lentigines	–	–	–	+	+
Hypertelorism	+	+	–	–	–
Deafness	+ (15–25%)	–	–	–	†
Male genital abnormalities	+ (38%)	+	–	–	†
HOCM	+	+	–	–	–
Pulmonary valve stenosis	+ (40%)	+	–	–	†
Cardiac tumour	*	–	–	–	+
GIT polyposis	–	–	–	+	–
Café au lait patches	+ (19%)	+	+	+	+
Growth retardation	+	+	+	–	–

+ = a well described association, – = not a recognised association, * one reported case, † not a previously reported feature but present in the family discussed under ‘Differential diagnosis’.

NEUROFIBROMATOSIS TYPE 1 (NF1)
LEOPARD syndrome has features in common with NF1.³¹ However, the skin findings differ and the number of true café au lait patches do not usually fulfil the diagnostic criteria for NF1. In 1996, Wu *et al*³² reported a de novo missense mutation in exon 18 of the NF1 gene in a woman with possible LEOPARD syndrome. She had multiple lentigines, mild mental retardation, and both valvular and subaortic stenosis. In the review of 80 cases by Voron *et al*¹⁰ valvular aortic stenosis was not described, hence this is atypical. In addition, the patient was not deaf. She lacked neurofibromas and Lisch nodules and therefore features were also not typical of NF1. This finding is yet to be repeated in a patient with classical LEOPARD syndrome. In cases 1 to 5, mutations were looked for in 6.6 kb of the NF1 cDNA but were not found (Dr Lois Mulligan, CRC, Human Cancer Research Genetics Group, Cambridge, personal communication, 1993).

Watson syndrome (café au lait spots, atypical pulmonary valve stenosis, and learning difficulties)²⁶ has phenotypic features common to both NF1 and LEOPARD syndrome. Mutations in the NF1 gene have been shown in patients with this condition.^{33 34}

PEUTZ-JEGHER SYNDROME (PJ)
It is easy to confuse these two conditions because gastrointestinal symptoms are not always present, particularly in childhood, and the lentigines may appear similar. However, in Peutz-Jegher syndrome the lentigines are also

Figure 3 Patient with NAME syndrome. The lentigines are very similar to those in multiple lentigines syndrome, but the distribution differs as buccal mucosa is involved.

present on mucosal surfaces. Patients with PJ syndrome, however, lack the coarse facial appearance and characteristic ECG seen in patients with LEOPARD syndrome.

NAME SYNDROME (NAEVI, ATRIAL MYXOMA, MYXOID NEUROFIBROMATA AND EPIPHILIDES/ENDOCRINE NEOPLASIA)
Multiple dark macules occur in this condition with a similar appearance to freckles (fig 3). Mucosal involvement and the lack of dysmorphic features characteristic of LEOPARD syndrome help the clinician to differentiate these diagnoses; 60% of patients manifest subcutaneous myxomas, most commonly on the eyelids, pinnae, and nipples. Half of patients develop intracardiac myxomas, usually biatrial, but some are intraventricular. Endocrine neoplasia occurs in 15–30%.^{25 35}
The authors were recently consulted by a family with NAME syndrome who were misassigned as LEOPARD syndrome until routine cardiac follow up showed an atrial myxoma. Several features of LEOPARD syndrome were noticed in those who had lentigines; these included sensorineural deafness, valvular pulmonary stenosis, innocent heart murmurs, winged scapulae, glandular hypospadias, café au lait patches, moderate learning difficulties, hypermobile joints, kyphoscoliosis, pectus excavatum, and prognathism.

We would like to thank Dr L Mulligan for molecular investigation of patients with LEOPARD syndrome and Dr A P Salmon for discussions regarding the cardiac features.

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