The heart in lentiginosis

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Three children with classical lentiginosis and cardiac involvement are described. Full investigation and two subsequent necropsies confirmed that the heart disease was due to severe hypertrophic obstructive cardiomyopathy.

Lentiginosis or hyperactivity of the melanocytes in skin presents in children as multiple small pigmented spots and thus may be erroneously diagnosed as von Recklinghausen's disease (Moynahan, 1962), but there are no neurofibromata and there may be other associated systemic disturbances such as somatic infantilism, short stature, and cardiac abnormalities. Walther, Polansky, and Grots (1966) described a family with lentiginosis, abnormal electrocardiograms, and systolic murmurs; they suggested that the cardiac abnormalities were due to a familial disorder of the conducting system, as did Matthews (1968). A patient with typical lentiginosis was fully investigated in the National Heart Hospital in 1967 and was shown to have classical hypertrophic cardiomyopathy; these findings were reported by Moynahan and Polani (1968) and Moynahan (1970). Recently, at the Dermatological Section of the Royal Society of Medicine (Moynahan, 1970) it was suggested by one of us that patients with lentiginosis should be regularly assessed by the cardiologist, and even in the presence of a near normal electrocardiogram and normal findings on right heart catheterization, a guarded long-term prognosis should be given as these findings do not exclude the presence or subsequent development of cardiomyopathy. The purpose of this study is to document the cardiological findings as not much attention has been given to this in previous communications.

Case reports

Case 1 A boy who died at age 16 years was the ninth of 12 children. The birthweight was 3854 g. He fed poorly, did not gain weight, and was subject to sweating and throbbing attacks for the first two years of life. A murmur was heard at 1 year, and because he only weighed 6.8 kg, he was

investigated for failure to thrive but no cause was found. His appearance was said to be normal and a photograph was taken at this time (Fig. 1). The heart was reported then to be large but the x-rays have been destroyed. A loud systolic murmur at the left sternal edge with low-pitched diastolic murmur suggested the diagnosis of ventricular septal defect; triple rhythm was mentioned, as was the diagnosis of Ebstein's anomaly. Electrocardiograms showed right ventricular and right atrial hypertrophy at this admission (Fig. 2). At age 4 years cardiac catheterization confirmed normal right heart pressure without shunts or gradients, but the electrocardiogram showed an in-

FIG. 1 Photographs of Case 1. (A) At age 1 year when he was undersized but had no brown spots. (B) Age 4 years showing lentiform moles on neck and chest and protuberant anterior chest (shown by permission of Professor J. Goodwin).

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FIG. 2 Electrocardiograms from Case 1 at ages 1 year, 4 years, and 15 years. Right ventricular hypertrophy was present at age 1 year which was more obvious at 4 years when left ventricular hypertrophy had also developed. By 15 years the electrocardiogram showed left axis deviation, P mitrale, and P pulmonale, and important left ventricular hypertrophy with giant voltage in left chest leads – aVR still showed evidence of right ventricular hypertrophy.

increase in right ventricular voltage with possibly left ventricular hypertrophy (Fig. 2). The A wave was prominent and phonocardiography showed an ejection systolic murmur with atrial and ventricular sounds. Many brown moles had appeared on the neck and trunk by this time (Fig. 1). At age 5½ years he was admitted with fits and a febrile

illness considered to be meningoencephalitis; a coincidental diagnosis of von Recklinghausen's disease was also made. Then more brown spots appeared in crops over the neck, trunk, perineum, and limbs. He was breathless on effort at 6 and had effort angina at 11. The diagnosis of lentiginosis was made by Dr. E. Moynahan at 10. In view of increasing cardiomegaly and symptoms, he was admitted in 1967 when aged 14. By this time the electrocardiogram showed obvious biventricular hypertrophy (Fig. 2). Cardiac catheterization (Table) with angiocardiology confirmed obstructive cardiomyopathy with gross septal hypertrophy (Fig. 3) and some mitral regurgitation. Propranolol reduced the gradient across the left ventricular outflow tract from 60 mmHg to 48 mmHg under anaesthesia – no isoprenaline was given as the heart was so grossly diseased.

At this time he had mild Madelung's deformity of the wrists, a bone age of 11, and a small pituitary fossa. He was below the 3rd percentile for weight and on it for height. There was an anteriorly bowed sternum with bilateral Harrison's sulci, and elbows which would not fully extend. A biopsy of skin showed melanin deposition in the inner layer of epithelial cells, reported by Dr. E. Moynahan to be typical of lentiginosis.

His angina increased and hepatic pain became troublesome so it was decided to see if resection of the septal muscle would improve him. Mr. Keith Ross explored the heart on bypass. The coronary arteries were found to be larger than usual and the cavity of the right ventricle was slit-like due to septal hypertrophy. Septal muscle was resected from the right and left side, but after this the heart would not support an adequate circulation.

Necropsy confirmed the presence of hypertrophic cardiomyopathy, the heart weighing 950 g. Histology and histochemistry of septal muscle at Royal Postgraduate Medical School by Dr. Eckhardt Olsen and Miss S. van Noorden showed classic features of severe hypertrophic cardiomyopathy.

Examination of 10 of his 11 sibs and mother with chest radiography and electrocardiograms showed no abnormality or pigmented spots. Father died in congestive heart failure at the age of 58. The necropsy report stated that his heart was enlarged and compatible with the diagnosis of cor pulmonale and systemic hypertension; no spots were commented on.

TABLE Catheterization data from 2 patients with lentiginosis

	Age (yr)	Pressures (mmHg)						
		PCV	PAP	RV body	RA	Aorta	LV	PA satn %
case 1	14	a = 13 v = 14	22/9	35–47/4	a = 10 v = 9	95/55	155/13	64
case 2	4	—	—	125/–135/5	A = 15	100/50	—	68
—	13	A = 15	25/10	40/8	A = 16	98/60	130/0	61
after isoprenaline:	—	—	22/10	50/6	A = 16	95/60	205/0	—

FIG. 3 Selective angiocardigrams from Case 1. (A) Right ventricular injection AP view showing gross septal enlargement bulging into the right ventricular cavity. (B) left ventricular injection lateral view showing gross septal hypertrophy in subaortic region. (C) Left ventricle AP view with extreme free wall hypertrophy. Large left coronary artery seen 'end on' in pulmonary area.

Case 2 This was a female full-term first child, of young parents birthweight 3600 g, result of a normal pregnancy. At 5 days a murmur was heard, the baby was breathless, and in heart failure, requiring digitalis. Weight gain was very slow and a continuous murmur with bounding pulses suggested a persistent duct. The chest radiograph showed slight cardiomegaly and the electrocardiogram suggested left ventricular dominance (Fig. 4). The child remained undersized but not in heart failure, and at 4 months a large duct was ligated by Mr. David Waterston. A thrill at the base of the heart, probably aortic, was felt after duct ligation. She recovered quickly but during the next two years had recurrent severe respiratory infections and failed to thrive. The long ejection systolic murmur remained (Fig. 5) but the electrocardiogram showed increasing right ventricular hypertrophy. The pulse was said to be jerky 'as if she still had the duct'. At 2 she was thought to be slow in mental development and was found to be severely deaf with deficient air and bone conduction but probably of normal intelligence. A systolic and diastolic murmur at the left sternal edge were obvious. In view of the development of severe right ventricular hypertrophy on the electrocardiogram (Fig. 4), cardiac catheterization was performed at age 4 years. A right atrial A wave of 15 mmHg and right ventricular pressure of 135/100/10 mmHg were found. Neither the left atrium nor pulmonary artery was entered and the femoral artery pressure was 100/50 mm Hg. A venous angiocardigram was said to confirm pulmonary stenosis. Skin pigmentation on the body was commented upon at

this time and von Recklinghausen's disease was diagnosed. The rubella syndrome was queried but antibodies were not present in the serum.

At 5, on bypass, Mr. Waterston found the right ventricle was huge, and on opening the pulmonary artery, the pulmonary valve was seen to be normal, and a thin-walled infundibular chamber was present with a tight infundibular stenosis underneath, caused by very hypertrophied muscle with thick endocardium. Large quantities of hypertrophied muscle and endocardium were resected. Recovery was uncomplicated. After this a severe scoliosis developed and the right ventricular hypertrophy pattern on the electrocardiogram persisted though the large P pulmonale diminished after 6 months (Fig. 4).

She remained below the 3rd percentile for height and weight (Fig. 6). From age 8½ more lentiform moles appeared under the chin and neck, on the inner surface of arms, body, and legs, in that order. A sublingual cyst was removed and she remained well until 12 when she became breathless on effort and more cheasty. The cardiac diagnosis was considered to be pulmonary regurgitation and stenosis.

At 13½ she was still below the 3rd percentile for height and weight (Fig. 7). Muscular development was poor and there were no secondary sex characteristics. Deep brown freckles were present on all unexposed parts (Fig. 8) and she had a severe kyphoscoliosis.

The arterial pulse was jerky and there was a large A in the jugular venous pulse. The scoliosis made recognition of ventricular hypertrophy difficult but the apex was in the anterior axillary line.

FIG. 4 *A and B* Electrocardiograms from Case 2. At 5 weeks there was left dominance, but right axis deviation had appeared by 7 weeks. One month after duct ligation there was probable right ventricular hypertrophy present in aVR which progressively increased to a severe degree by 3 years. The P pulmonale disappeared after infundibular resection and the degree of right ventricular hypertrophy remained severe up to age 12 years.

There was an ejection murmur in the pulmonary area and apex, and a loud delayed diastolic murmur which increased at the left sternal edge on inspiration, with atrial and third sounds, and the second sound was single (Fig. 5). Her immature mind and body in association with freckles in unexpected places suggested the diagnosis of lentiginosis, with hypertrophic obstructive cardiomyopathy to account for the heart size and signs.

The electrocardiogram still showed severe right ventricular hypertrophy with increasing left-sided voltage. Cardiac catheterization showed no shunts and a gradient of 25 mmHg across the right ventricular outflow tract under general anaesthesia and 15 mmHg across the left ventricular outflow tract. The femoral arterial and central aortic pressure pulses had a sharp upstroke. After a small dose of intravenous isoprenaline, the heart rate rose from 130 to 180 and the gradient across the left ventricular outflow tract rose from 15 to 125 mmHg (Fig. 9), and a pull-back of the catheter in the pulmonary artery showed a gradient of 45 mmHg low in the right ventricular outflow tract (Fig. 9). Intravenous propranolol 2.5 mg reduced the gradient across the left ventricular outflow to 5–10 mmHg and 8 mmHg across the right ventricular outflow (Fig. 9). Left ventricular and right ventricular biplane Elema angiocardigrams were done showing extreme thickening of the ventricular septum bulging into both ventricular cavities and some free wall and papillary muscle hypertrophy on the left, as in Case 1 (Fig. 10).

It was decided to treat her with propranolol 20 mg b.d. in an attempt to prevent increasing obstruction and to give diuretics if congestive features appeared. Skin biopsy of the forearm was reported by Dr. Moynahan to be typical of lentiginosis. Re-examination of the skin taken at age 4 years, which had been reported on as von Recklinghausen's disease, was now considered to be typical of lentiginosis.

Case 3 A boy who died at age 14 years was born 3 weeks postmature weighing 3288 g. He was a poor feeder, and at 2 weeks was found to have a systolic murmur. Examination at age 1 month showed a harsh systolic murmur, a heart of normal size, and an underweight baby.

The child developed slowly and was small for his age. By 5, he had right biventricular hypertrophy and brown pigmented spots. Cardiac catheterization showed a gradient of 30 across the right ventricular outflow tract, with an increase of the wedge pressure, suggesting mitral regurgitation. A concomitant diagnosis of pulmonary stenosis was made. He was considered to have von Recklinghausen's disease. By the age of 10, he had dyspnoea and increasing numbers of brown spots, and the electrocardiogram was bizarre, suggesting biventricular hypertrophy (Fig. 11).

His appearance with somatic infantilism resembled Case 1. He died suddenly at school. Necropsy report by Professor A. Claireaux commented on the small size of the child aged 14, weight 27.67 kg and length 142 cm, with many brown spots on face, trunk, and limbs, varying from 1–10 mm in diameter. The skull had a deficiency in the outer table of the right temporal region. The heart weighed 429 g and was mainly due to left ventricular hypertrophy, with bulging of the thick septum into the right ventricle. The coronary arteries and valves were normal and the foramen ovale was narrowly patent. Histology of cardiac muscle showed large fibres varying in size with whorls and large nuclei seen

FIG. 5 Phonocardiograms from Case 2. (A) At 18 months showing intense ejection murmur and presystolic murmur at the left sternal edge with loud aortic valve closure. (B) Age 13 years, less prominent ejection murmur but presystolic murmur still obvious. Abnormal left ventricular movement recorded.

in hypertrophic myopathy (van Noorden *et al.*, 1971). The skin had melanin deposits in the inner epithelial layer.¹

Discussion

In these patients, the diagnosis of lentiginosis was confirmed by skin biopsy which showed characteristic clumps of hyperactive melanocytes, with pigment going from the basal layer into the dermis and associated with corrugation of the epidermis. The distribution of pigment was the same as in other reported cases, unrelated to sunlight exposure, and sparing the face but not the palms of the hands.

Angiocardiography in two patients showed that the cardiac diagnosis was hypertrophic cardiomyopathy of a most severe form; necropsy confirmed the diagnosis in Cases 1 and 3. Cardiac muscle biopsy from the living heart in Case 1 showed characteristic and extreme histological and histochemical changes described in patients with hypertrophic cardiomyopathy (van Noorden, Olsen, and Pearse, 1971).

In all these 3 patients, heart disease was clearly well established in the first year of life as shown by murmurs, cardiomegaly, and abnormality in the electrocardiograms. It is unusual for there to be evidence of florid cardiac disease during infancy in patients who later are shown to have obstructive myopathy though hypertrophic cardiomyopathy has occasionally been found in a stillborn and neonate (Neufeld, Ongley, and Edwards, 1960). Whether the thriving problems were related to true heart failure is unknown. There

is no confirmatory evidence of heart failure or that digitalis did any good. It is most unusual for a congestive phase to precede an obstructive phase in hypertrophic myopathy and, unless it did, digitalis would be unlikely to be beneficial, so the use of this drug cannot be taken as evidence of cardiac failure at this time. The duct in Case 1 may have caused the

FIG. 6 Percentile charts showing development of Case 2. (A) Weight remains below normal percentiles and from 9 years falls even further away from normality. (B) Height remains below normal percentiles after first month and falls further away after 10 years showing very slow growth. Slight loss of height may be related to kyphoscoliosis.

¹ Data complete but inaccessible.

FIG. 7 Physique of Case 2 at age 13 years showing no secondary sex characteristics, poor skeletal muscular development, and ageless face.

heart failure but treatment of it made little difference to the growth curve. It is presumed that this was a coincidental anomaly, though

FIG. 8 Characteristic lentiform moles on arms of Case 2.

it is known that congenital heart disease may coexist with obstructive cardiomyopathy (Somerville and McDonald, 1968).

Usually in hypertrophic obstructive myopathy, left-sided signs and appropriate electrocardiographic features dominate the clinical picture, but in these patients with lentiginosis, severe right ventricular hypertrophy and right-sided signs have been present early and thus suggested the diagnosis of pulmonary stenosis. This diagnosis was made in all, and once labelled as such it was many years before the true diagnosis was made. The right ventricular obstruction in Case 2 was clearly severe by age 4 years, with right ventricular pressures at systemic level, thus demanding surgical attention. It is probable, on looking back, that bulging septal muscle was causing the obstruction and not a fixed organic collar-like infundibular obstruction. Certainly, resection of this muscle relieved the right ventricular hypertension and strain on the right side, as evidenced by loss of P pulmonale and reduced right ventricular pressure 9 years later, but it is doubtful if it made any difference to the subsequent course of the disease. It is likely that the subsequent development of left ventricular hypertrophy is responsible for the later symptoms and the sudden death that occurred in Case 3.

Thus it is seen that early involvement of the right side of the heart may give rise to the erroneous early diagnosis of pulmonary stenosis as in reported patients (Lewis *et al.*, 1958; Walther *et al.*, 1966; Matthews, 1968). The finding of resting gradients in the right ventricular outflow adds further support to the diagnosis of organic pulmonary stenosis and, without angiocardiology, the true diagnosis of septal hypertrophy cannot be made. Indeed, if left-sided pressure studies, without angiocardiology, are undertaken, the diagnosis of combined organic subpulmonary and subaortic stenosis may be made (Kraunz and Blackmon, 1968). The normality of left-sided pressures at rest is to be expected early in the disease, and the true underlying myopathic process may not be uncovered unless isoprenaline is given to promote gradients in the outflow tract and left ventricular angiocardiology reveals the unusual anatomy of the left ventricle. Aortography understandably used by others to exclude coronary artery abnormalities in the presence of strange electrocardiograms in association with lentigo, will not help to make the true diagnosis of hypertrophic cardiomyopathy. Retrospectively, it is most likely that cardiomyopathy was present in a milder form in the families described by Walther and his colleagues (1966) and Mat-

thews (1968), as well as in Macmillan and Vickers' patient (1969) and some of Gorlin, Anderson, and Blaw's cases (1969). The electrocardiograms illustrated are compatible with this diagnosis, and it is of note that Walther considered 'hypertrophic sub-aortic stenosis' in the differential diagnosis.

It is interesting to consider the relation of the syndrome of severe pulmonary valve stenosis, pigmented spots, and dull intelligence described by Watson (1967), to that of lentigo and cardiomyopathy. Though it is possible that some of Watson's patients had excessive muscular hypertrophy, the diagnosis of severe pulmonary valvar obstruction was confirmed by necropsy in 2, and both had severe infundibular hypertrophy, which was probably secondary to the organic obstruction, there being therefore no reason to postulate a coexistent myopathy. The inheritance of the pigmented spots in Watson's 3 families was the same as in the patients with lentiginosis (Walther *et al.*, 1966; Capute, 1969; Matthews, 1968), but pigmented spots are different histologically from lentigo. It is thus probable that Watson's syndrome is related but distinct from cardiomyopathy and lentiginosis. Similarly, the familial syndrome with deafness, skeletal immaturity, and pulmonary stenosis described by Lewis *et al.* (1958) and added to by Koroxenidis *et al.* (1966) may also be related to cardiomyopathic lentiginosis, but until the actual chemical or enzymatic disturbance is identified this must remain uncertain.

It appears from the reported cases of lentiform moles and cardiac involvement that there are two forms of the disease – mild and slow in development and a severe florid type. The familial patients reported by Capute (1969) and others appear to have the milder form which by definition can survive to breed. Sporadic examples with mild cardiac involvement have also been reported by Pickering *et al.* (1971) who retrospectively reviewed their data after seeing ours at the Royal Society of Medicine and thought cardiomyopathy was a most likely explanation. This is in contrast to the 'sporadic' examples reported here, which have obvious cardiac manifestations early and are in trouble or dead at the time of expected puberty. Such patients would not live long enough to breed, but one wonders if with the obvious somatic infantilism they would be even able to breed. No hormonal studies were made but no secondary sex characteristics had appeared in any of these three patients.

The fundamental problem is the relation between the development of the hypertrophic cardiomyopathy and the lentiginoses. The

FIG. 9 Pressure tracings from Case 2 showing response to isoprenaline. (a) Shows large gradient (120 mmHg) between left ventricle and aorta after isoprenaline without change in pulmonary artery pressure. (b) Response of pressure pulses to ventricular ectopics (after isoprenaline) showing slight increase in gradient and left ventricular pressure without fall of aortic pressure in the post ectopic beat. The infundibular pressure also increased after the ectopic beats. (c) (opposite) After 2.5 mg propranolol the gradient was reduced to 10 mmHg across the left and right outflows. After a single ventricular ectopic, there was a slight increase in gradient, but the aortic pressure fell 5 mmHg and the infundibular pressure rose.

usual patient with hypertrophic obstructive cardiomyopathy, whether familial or sporadic, does not have multiple brown spots, which suggests there is a different aetiology, even though the physiological and gross pathological findings appear the same. Another interesting feature is that there was worsening of the cardiac problem with the increased numbers of lentiform moles, and both worsened quickly after age 10 years. All signs became more obvious after the lentiform moles started to appear at 2 to 3 years, but we have no yardstick to measure and compare the rate of heart muscle growth. Whether the heart muscle was abnormal at birth or at 6 months is unknown, but the cardiac myopathy was established by age 1 year in Case 1, whose electrocardiogram was then very abnormal, and was present from the described physical signs at 4 months at the time of duct ligation in Case 2, and also obvious at 3 months in Case 3. Moynahan has suggested that there is some upset in development of the neural crest cells which would explain the pigmentation, some of the generalized abnormalities, and possibly the heart problem, though this is difficult to accept.

Another possibility is that there is a metabolic chemical or enzyme upset which may result in excessive pigmentation and excessive cardiac muscle hypertrophy. The chemistry of melanin in the skin and noradrenaline in the heart is closely related so it is possible there is upset in control in the precursors.

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Pearse (1964) originally suggested that there was excess noradrenaline in heart muscle of patients with hypertrophic obstructive cardiomyopathy; but this has now been found to be nonspecific, and also occurs in hypertrophied left ventricular muscle associated with aortic stenosis and other conditions (Kristinsson *et al.*, 1970). The possible stimulus to cardiac muscle hypertrophy in lentiginosis does not affect skeletal muscle, as electromyography in

FIG. 10 Angiocardiograms from Case 2. (A) Right ventricular AP view showing some septal hypertrophy but much wider outflow than in Case 1. (B) Left ventricular AP view (systolic) showing septal and free wall hypertrophy with normally opening aortic valve. (C) Diastole showing persistent subvalve narrowing with massive septal hypertrophy.

Case 2 was found to be normal by Dr. R. Kozyen.

Not only has the skin condition often been wrongly labelled as von Recklinghausen's disease initially, but also the heart condition has remained undiagnosed until late. It is suggested that in any patient with lentigo and heart murmurs, cardiomyopathy is the first diagnosis to be considered. Furthermore, any patient with lentiform moles should have cardiological assessment at regular intervals, as in the milder form the heart involvement may not appear until later, and even a normal right heart catheter should not be considered to exclude the diagnosis or the possibility of subsequent development of cardiomyopathy.

Careful cardiac assessment of patients with lentigo may lead to recognition of the early signs and physiology of obstructive myopathy before the usual florid features are obvious and thus contribute to our knowledge and understanding of the pathogenesis of this complex condition.

Dr. E. Moynahan made the dermatological diagnosis in Cases 1 and 3, and confirmed the diagnosis after biopsy at cardiac catheterization in Case 2. Dr. Eckhardt Olsen has looked at the sections of heart muscle which made the histopathological diagnosis and we are indebted to him. We thank Professor J. Goodwin for allowing us access to his early notes on Case 1 and for permission to publish the relevant data.

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FIG. 11 Electrocardiogram from Case 3 when aged 8 years shows important biventricular hypertrophy, particularly shown in aVR and aVL. There is also characteristic and pathological left axis deviation.

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