Familial neurofibromatosis and hypertrophic cardiomyopathy

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SUMMARY Two siblings from a family in which neurofibromatosis was inherited as an autosomal dominant had hypertrophic cardiomyopathy and neurofibromatosis. Idiopathic hypertrophic cardiomyopathy may have occurred by chance in two first degree relatives with neurofibromatosis. An alternative explanation is that these diseases are both manifestations of a common hereditary defect of neural crest tissue. Another possibility is that abnormalities of catecholamine metabolism and nerve growth factor in neurofibromatosis can cause secondary ventricular hypertrophy with septal involvement.

The aetiology of hypertrophic cardiomyopathy is unknown, although genetic factors are almost certainly involved. In addition, there is increasing evidence, both clinical and experimental, of an abnormality of catecholamine metabolism. Reports of abnormal catecholamine metabolism in neurofibromatosis have led to the suggestion that there is an aetiological link between the two diseases.

Case reports

CASE 1
The index case (II.2, age 42) presented with exertional chest pain and a systolic murmur (figs 1 and 2a). There was a past history of peptic ulceration. The resting electrocardiogram showed considerable left ventricular hypertrophy. Cross sectional and M mode echocardiography (fig 2b and c) showed hypertrophic cardiomyopathy with asymmetric septal hypertrophy. The interventricular septum was 2-8 cm thick, and the posterior left ventricular wall was 1-2 cm thick. In systole there was pronounced anterior motion of the mitral valve and obliteration of the left ventricular cavity. Cardiac catheterisation and angiography showed normal coronary arteries, and a left ventricular outflow gradient of 70 mm Hg. Radionuclide ventriculography showed an ejection fraction of 70%.

Fig 1 The family pedigree.
I.1 Father of propositus, known to have NF, died aged 64 of carcinoma of stomach; I.2 mother of propositus, alive and well, aged 74, no clinical evidence of NF or HCM; II.1 sister of propositus, aged 49, classic NF and HCM; II.2 propositus, classic NF and HCM, aged 47; II.3 brother of propositus, known to have NF, aged 46, refused examination; III.1 woman aged 26, known to have NF, refused examination; III.2 woman aged 25, examined—normal; III.3 man aged 19, classic NF, heart normal; III.4 woman aged 24, reported normal, refused examination; III.5 girl aged 5, NF of typical cafe au lait type, heart normal; III.6 boy aged 4, classic NF, heart normal; III.7 boy aged 9, reported NF; parents refused permission for examination; III.8 girl aged 6, reported NF (as III.7); IV.1 girl aged 7, reported NF of typical cafe au lait type (as III.7); IV.2 girl aged 4, normal at examination; IV.3 boy aged 3, reported normal, refused examination. NF, neurofibromatosis; HCM, hypertrophic cardiomyopathy.

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fraction of 100°, and typical features of hypertrophic cardiomyopathy. Biopsy of the skin nodules confirmed neurofibromatosis. Concentrations of plasma catecholamines and urinary catecholamine metabolites were normal. Serum concentrations of calcium and fasting gastrin were also normal.

CASE 2
The 46 year old sister of case 1 has severe kyphoscoliosis, large numbers of neurofibromas, and giant café au lait patches (fig 3a and b). Cardiovascular examination and resting electrocardiography were normal but the chest x ray showed a right paravertebral neurofibroma. Her thoracic deformity hampered echocardiography but an apical four chamber cross sectional view showed evidence of hypertrophic cardiomyopathy (fig 3d and e) with subaortic septal hypertrophy. Cardiac catheterisation and angiography showed normal coronary arteries with a grossly abnormal left ventriculogram. There was a “ballerina foot” deformity with mid-cavity obliteration and an ejection fraction of 70°. No intracavity gradient was found. Left and right heart pressures were normal. Concentrations of plasma catecholamines and urinary metabolites were normal.

THE FAMILY
The family consisted of the index case (II.2), six first degree, and nine second degree relatives. With the exception of the index case and his sister all those examined had normal hearts. Four first degree and
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Discussion

Cross sectional echocardiography showed hypertrophic cardiomyopathy in the index case (II.2, fig 2b) and his sister (II.1, fig 3d and e). Both had considerable asymmetric hypertrophy of the interventricular septum. There was evidence of obstruction of the left ventricular outflow tract in case II.2 which was confirmed at catheterisation, but this feature was not present in his sister (II.1). Neurofibromatosis has been misdiagnosed as lentiginosis. Our diagnoses were confirmed by biopsy of the skin nodules in case II.2 and by associated skeletal and dermatological findings in his sister (II.1).

Where neurofibromatosis is suspected in the absence of skin nodules, the diagnosis may be made by the finding of six or more café au lait skin patches of >1.5 cm². Neurofibromatosis was diagnosed in this way in cases III.5 and IV.1.

The association between hypertrophic cardiomyopathy and neurofibromatosis has already been reported. The cells responsible for the neurofibromas are of neural crest origin and it may be relevant that other neuro-ectodermal conditions have been reported in association with hypertrophic cardiomyopathy. The best known of these is lentiginosis, where the melanocytes responsible for the

Fig 3  (a) Anterior view of case II showing typical cutaneous neurofibromas. (b) Lateral view of case II showing the severe degree of kyphoscoliosis. (c) Posterior anterior chest radiograph of case II showing the severity of her skeletal deformity and a large neurofibroma in the right upper zone (arrows). (d) Apical five chamber cross sectional echocardiogram from case II showing pronounced subaortic hypertrophy of the septal myocardium (arrows). (e) Apical four chamber view in case II showing a pronounced septal bulge above the mitral valve. AV, aortic valve; IVS, interventricular septum; LA, left atrium; LV, left ventricle; MV, mitral valve; RA, right atrium; RV, right ventricle; TV, tricuspid valve.
skin lesions arise from the neural crest. Two studies have indicated that the association of hypertrophic cardiomyopathy and lentigiosis might be familial and autosomal dominant, but other family studies have failed to confirm this. Hypertrophic cardiomyopathy has been described with phaeochromocytoma and parathyroid tumours. Symons et al have studied this association. They showed that patients with hypercalcaemia caused by hyperparathyroidism may have asymmetric septal hypertrophy, and also that normocalcaemic patients with hypertrophic cardiomyopathy have raised concentrations of parathyroid hormone. They also showed that unexplained hypertrophy may also be found in thyrotoxicosis where sympathetic activity is increased. Tumours of the parathyroid, adrenal medulla, and medullary cells of the thyroid (all of neuro-ectodermal origin), occur together in the multiple endocrine adenoma syndrome type II, or Sipple’s syndrome. This is often autosomal dominant and has been reported in association with hypertrophic cardiomyopathy and with neurofibromatosis. Riccardi reported raised concentrations of catecholamines in neurofibromatosis. In at least two cases no phaeochromocytoma could be found and neurofibromas were thought to be the source.

There is increasing debate about the role of catecholamines in hypertrophic cardiomyopathy. Dense sympathetic innervation and high tissue catecholamine concentrations in the septal myocardium have been reported. Others have refuted this. The developing myocardium is known to be very sensitive to catecholamines, and in normal neonates circulating concentrations are already high. Experimental work by Olsen et al has shed some light on possible interactions in the developing myocardium. The administration of TRIAC (dithyramolamine salt of triiodothyronine), a triiodothyronine analogue, to pregnant rats produced widespread cellular disarray resembling that seen in hypertrophic cardiomyopathy. This reaction could be blocked by propranolol. Perloff suggested that a possible mechanism for the development of hypertrophic cardiomyopathy is that catecholamine abnormalities lead to cellular disarray. He postulated that the inherent isometric contraction of malaligned cells is less effective and leads to secondary myocardial hypertrophy. If Perloff’s theory is correct myocardial disarray with subsequent hypertrophy could be a secondary phenomenon in neurofibromatosis if catecholamine concentrations are abnormal during early development when the septum is known to be hypersensitive.

Other hormonal mechanisms may be involved. Nerve growth factor is a naturally occurring glycoprotein required for growth and maintenance of sympathetic and sensory neurones. Abnormal metabolism of this substance is thought to be a factor in the pathogenesis of neurofibromatosis and different forms of the disease are distinguishable by the circulating concentrations of nerve growth factor. Whereas sensory ganglia respond only during embryogenesis, when the influence of nerve growth factor is greatest, mature sympathetic neurones remain responsive to this factor. Imbalance of the delicate interaction between developing myocardium, sympathetic innervation, catecholamines, and nerve growth factor has been proposed as a model for the pathogenesis of hypertrophic cardiomyopathy.

We found hypertrophic cardiomyopathy and neurofibromatosis in two siblings. There are three possible explanations for this. Firstly, the two diseases could have appeared together by chance, although this seems unlikely. Both are relatively common conditions with a similar incidence, about 1:3000, although this figure is less certain in the case of hypertrophic cardiomyopathy. Secondly, left ventricular hypertrophy may be secondary to neurofibromatosis, perhaps as a result of abnormal metabolism of catecholamines or nerve growth factor. Thirdly, both diseases could be common manifestations of a defect of neural crest tissue with autosomal dominant inheritance.

The known coincidence of hypertrophic cardiomyopathy with conditions such as lentigiosis and hyperparathyroidism argues in favour of a common defect of the neural crest. This seems more plausible than secondary left ventricular hypertrophy in the presence of an abnormality of catecholamines or nerve growth factor, which may occur in neurofibromatosis. Furthermore, neurofibromatosis is independently associated with hyperparathyroidism and with Sipple’s syndrome, and the pattern of asymmetric septal hypertrophy seen in these two cases is indistinguishable from that seen in idiopathic hypertrophic cardiomyopathy.

There is circumstantial evidence suggesting a link between neurofibromatosis and hypertrophic cardiomyopathy. Abnormalities of catecholamine metabolism, sympathetic innervation, and nerve growth factor may account for the development of idiopathic left ventricular hypertrophy in certain subjects with neurofibromatosis. An alternative explanation, supported by the known association of both conditions with other diseases of neural crest origin, is that they are genetically linked. The sequence containing the gene for neurofibromatosis has recently been located by linkage analysis to polymorphic markers on chromosome 17. We speculate that this could lead to the identification of a genetic marker for hypertrophic cardiomyopathy.
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**References**

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