Congenital heart disease associated with hypertrophic cardiomyopathy

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SUMMARY Experience has shown that clinical hypertrophic cardiomyopathy (HOCM, ASH) occurs in some patients with congenital heart disease, particularly simple lesions with a good natural prognosis. Its presence should be suspected when the clinical course is atypical for the basic congenital lesion or when there is unexpected cardiomegaly, an associated left sided lesion or left ventricular hypertrophy in abnormalities which primarily affect the right side of the heart, or an atypical electrocardiogram showing QS patterns, left anterior hemiblock, deeply inverted septal T inversion, or unusual ST-T changes over the left ventricle.

Histopathologically, ‘myocardial dysplasia’, indistinguishable on light microscopy from HOCM, is common in many hearts with congenital cardiac lesions, particularly in the ventricular septum. It varies in extent, distribution, and site. Its presence may account for certain unpredictable changes in congenital heart disease.

The influence of ‘dysplasia’ on the clinical state in both isolated myopathy and when combined with congenital heart lesions depends on its extent and on the occurrence of secondary postnatal haemodynamic and biochemical disturbances. Myocardial dysplasia is probably congenital and common and it may be asymptomatic; pathologist and clinician should be aware of and search for it.

Progress in the management of congenital heart disease has been concerned with early diagnosis of mechanical abnormalities and the successful surgical treatment carried out increasingly earlier in childhood. Attention has been directed to the obvious structural deformity and the resultant circulatory disturbances. This approach has been rewarding but has probably delayed the recognition of coexistent congenital myocardial disease in some patients. When present, this not only can modify the clinical features but also may influence the course after successful surgical correction of the defect.

Now faced with a new medical community, namely the survivors of successful treatment for congenital heart lesions, we are seeing that there is more abnormality in the cardiovascular system than can be treated by the surgeon’s skill. There is accumulating evidence (Somerville and Becu, 1977b) that in patients with structural cardiac malformations the congenital abnormality is not always confined to valves, septa, and connections but may also affect the heart muscle, major conducting arteries, and even coronary arteries, and as such are examples of ‘congenital cardiovascular disease’ (Becu et al., 1976).

Hypertrophic cardiomyopathy in its various forms is obviously a congenital abnormality, often transmitted as a Mendelian dominant (Emanuel et al., 1971), and is a peculiar and bizarre abnormality of the heart muscle. The association of this mysterious disease with structural congenital heart abnormalities now requires reappraisal in the light of current knowledge.

Definition: hypertrophic cardiomyopathy and dysplasia

Damage to the myocardium in fetal life causes various histological changes in the hearts examined after birth, such as fibrosis, infarction, hypertrophy, necrosis, fibroelastosis, and ‘dysplasia’ in one or both ventricles.

The term ‘dysplasia’ is used to describe the histological appearance of the myocardium where the muscle fibres are malaligned, disordered,
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truncated, and ‘whorled’, associated with perinuclear vacuolisation, with such changes located most severely in the ventricular septum. These alterations in myocardial morphology are indistinguishable from those found in the different clinical forms of hypertrophic cardiomyopathy (Ferrans et al., 1972).

Further adaptive pathological changes may develop in the heart during the years after birth as a response to altered function, growth, or as a reparative process. Such changes may result in restoration to, or maintenance of, normal myocardial function or be associated with varying types of clinical ventricular dysfunction. The manifestations of disordered myocardial pathology in the living patient must depend upon whether hypertrophy, fibrosis, or new muscle formation occurs and in what combination, amount, and site.

In living patients, hypertrophic cardiomyopathy presents in different ways, variously described as ‘functional obstruction of the left ventricle’ (Brock, 1957), asymmetrical septal hypertrophy (ASH) (Teare, 1958), idiopathic hypertrophic subaortic stenosis (IHSS) (Morrow and Braunwald, 1959), hypertrophic obstructive cardiomyopathy (HOCM) (Goodwin et al., 1960), and more recently midventricular HOCM (Falicov and Resnekov, 1977).

In all these clinical syndromes the same basic myocardial disorder, namely severe ‘dysplasia’, is present on histological examination, but this varies in extent, distribution, and severity, accounting for the different clinical presentations. It is interesting that Paré et al. (1961) referred to the condition as ‘hereditary cardiovascular dysplasia’ which to us now appears to be a most appropriate name, showing a correct understanding of the disease. Here the term ‘hypertrophic cardiomyopathy’ describes the whole group who have the same basic histological disorder of the myocardium, namely ‘dysplasia’.

Incidence

Structural congenital heart disease occurs in about 1:100 births if stillborns are included (Mitchell et al., 1971). The incidence of ‘isolated’ hypertrophic cardiomyopathy in the general population is unknown. The coexistence of clinically obvious hypertrophic cardiomyopathy and congenital cardiac malformations (Somerville and McDonald, 1968; Shem-Tov et al., 1971) appears to be uncommon. When both are recognised in the same patient the myocardial disorder has to be severe to be noticed in the presence of congenital defects which influence the physical signs. Only 19 patients with both conditions have been identified during the past 15 years in the National Heart Hospital. This suggests that the association is rare, below 1 per cent of congenital cardiac lesions seen, and that it might be a coincidence.

Although pathologists have occasionally drawn attention to the abnormal myocardium in congenital heart disease (Berry, 1967; Franciosi and Blanc, 1968), myocardial dysfunction which cannot be explained by the obvious mechanical lesion tends to be ignored or is attributed to damage at the time of operation or to ischaemia in relation to chronic low cardiac output. We believe that if the possibility of congenital abnormalities of heart muscle, particularly dysplasia, were more frequently considered, the incidence of congenital heart disease with hypertrophic cardiomyopathy might be higher.

Recognition depends on criteria for diagnosis as well as awareness of the possibility. Mild cases may be missed particularly if unaware clinicians and pathologists do not search.

Types of congenital cardiac defects associated with hypertrophic cardiomyopathy

When congenital heart disease and hypertrophic cardiomyopathy occur together, the structural lesions reported are usually simple ones, such as secundum atrial septal defect, small ventricular septal defect, persistent ductus, pulmonary valve stenosis, aortic valve stenosis, and coarctation of the aorta. All these as ‘isolated’ lesions may have a reasonable prognosis which means there may be time for adaptive or reactive myocardial changes to develop.

Hypertrophic cardiomyopathy unassociated with structural abnormalities in the architecture of the heart can cause death in stillborns, newborns, and infants, but clinical manifestations usually appear later after survival has permitted secondary changes to occur in the myocardium. The same appears to be true when hypertrophic cardiomyopathy and congenital heart disease appear in the same patient. Most of the completely documented reports are in children over 5 years and more particularly in adolescents and adults. It must be said that knowledge of myocardial abnormalities particularly ‘dysplasia’ in infants with complex congenital anomalies is deficient. Observers’ eyes are fixed on the gross disorder of cardiac architecture and not on the myocardium. Perhaps study of the myocardium in stillborns and newborns dying with congenital heart disease might reveal interesting information on this. In our experience infarction, fibrosis, and ‘dysplasia’ do occur in the hearts of infants who die with truncus arteriosus, trans-
position, and common atrioventricular canal. The clinical contribution of such pathological processes is not yet defined.

**Diagnosis of hypertrophic cardiomyopathy in congenital heart disease**

Recognition of cardiomyopathy influencing the natural history of congenital heart disease is vital as its presence may spoil the results of surgical treatment as well as leaving an important clinical residuum. When there is added cardiomyopathy of importance the clinical picture does not perfectly fit the textbook description or natural history of congenital heart disease. For example, there may be unexpected dyspnoea, heart failure, or cardiomegaly in infancy which improves, or the finding of mitral regurgitation or subaortic stenosis in basically right-sided lesions such as tetralogy of Fallot, atrial septal defect, or pulmonary stenosis provides important clues.

An atypical electrocardiogram appears to be the best guide to the presence of serious additional myocardial disease. Such findings as left anterior hemiblock in a lesion not usually associated with it or extensive and unexpected steep T wave inversion over the left ventricle particularly over septal leads, and QS patterns or the absence of predicted hypertrophy patterns should suggest extensive myocardial dysplasia.

Angiocardiography shows bizarre appearances of the left and sometimes the right ventricular cavity. It is mandatory that in right-sided lesions with any of these unusual features the diagnosis of clinical cardiomyopathy is suspected before invasive investigations are done so that the correct tests and angiocardiograms are performed.

Final confirmation of the diagnosis of hypertrophic cardiomyopathy has tended to rely predominantly upon gross macroscopical appearances at necropsy and the allegedly characteristic histological features of HOCM and ASH. However, we believe that histology and electron microscopy are of value only if the clinical and haemodynamic findings are consistent with the gross appearance of the heart. Indeed, microscopy may be misleading if the more obvious evidence is lacking since 'dysplasia' may be found frequently in congenital heart disease as well as occasionally in the heart muscle in rheumatic heart disease (Dingemans and Becker, 1977).

**Problems**

Although our studies have shown that dysplastic muscle is common particularly in the cephalad part of the ventricular septum in congenital heart disease we do not know what its contribution is to clinical disease and dysfunction in the living. We doubt if a little dysplasia in the ventricular septum is of importance. Dysplasia perhaps has the potential to influence the haemodynamics and natural history when present in critical amounts or if certain stresses occur. Though dysplastic muscle is also present in the right ventricle in isolated clinical hypertrophic cardiomyopathy this is a disease which mainly affects the left ventricle.

In order to examine the problem of dysplasia and hypertrophic cardiomyopathy in congenital heart disease, the hearts and clinical features of patients with 'isolated' or simple pulmonary valve stenosis were studied since only the right ventricle should be affected by mechanical stresses. Careful sectioning of both ventricles, septa, aorta, and coronary arteries in 25 specimens mainly from infants under the age of 2 years showed that there were large areas of 'dysplastic' myocardium indistinguishable from HOCM, not only in right ventricular muscle but also in the left ventricle and septum, in 25 per cent (Becú et al., 1976). In 51 patients there was obvious severe macroscopical abnormality of the left ventricle and ventricular septum yet no structural valve lesion was present to account for such changes. Retrospective review of the clinical course of dead patients showed that these gross pathological changes in left ventricular myocardium clearly had had clinical effects. The extensive dysplasia in the myocardium must have been congenital since it was also present in some newborns. In another series of living patients treated by pulmonary valvotomy, 15 per cent had suggestive clinical evidence of left ventricular dysfunction and even pulmonary oedema was seen after operation for no obvious reason. One of these patients reinvestigated 8 years later had clinical and angiographic features of hypertrophic myopathy affecting the left ventricle. Routine angiocardiographic investigation of left ventricular function in 39 patients with simple pulmonary valve stenosis has also shown that the left ventricular ejection fraction is unusually high in about 20 per cent and unusually low in 8 out of 10 children under 2 years at the time of operation (Sa'e Melo and Somerville, 1977, unpublished observations).

It is interesting that left ventricular studies in simple pulmonary valve stenosis have been used to establish the normal values for left ventricular function in children (Miller and Swan, 1964). We now believe that this was an unwise choice for normal standards. However, our major difficulty in relating myocardial function to pathological changes is that we do not know the extent of these changes in...
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the ventricular muscle in the living, though study of myocardial biopsy material from the infundibular septum has shown severe dysplasia to be most obvious in those who retain large infundibular gradients after valvotomy.

The aortic media in hearts with pulmonary valve stenosis also showed severe disorientation of the muscular and elastic fibres of the media described as 'higgledy piggledy' arteriopathy and there were frequently lesions in the coronary arteries not related to the severity of myocardial or aortic changes. Such findings surely support the concept of congenital cardiovascular disease which may be present in pulmonary valve stenosis. Indeed, the same aortic changes have also been found in infants and children presenting with systemic hypertension without other congenital heart disease (Becú and Gallo, 1974), in the various congenital syndromes manifesting as supra-aortic stenosis (Somerville and Becú, 1977a), in association with other congenital valve abnormalities including 'thick semilunar valve stenoses' (Somerville and Ross, 1977), and occasionally in patients with isolated hypertrophic cardiomyopathy. It is of note that systolic hypertension may occur with all these lesions, and might be related to conduction of the pulse wave down the abnormal central arteries.

As already stated, the clinical effects of the congenital dysplasia both in the muscle of the heart and in the media of the conducting arteries are really unknown. For the myocardium, the answer probably depends upon the severity and extent of the myocardial dysplasia, necrosis, and fibrosis, and what secondary factors are added. These secondary changes must be influenced by many factors such as stimuli to secondary hypertrophy from a valve obstruction or hypertension, athletic way of life, or altered catecholamine excretion, and all of the above may influence the outcome but are difficult to quantify. Just as in patients with 'isolated' hypertrophic cardiomyopathy the clinical effects are many and different, so are the effects of myocardial dysplasia in congenital heart disease.

Since we now know that many congenitally abnormal hearts contain large areas of dysplastic myocardium, it is justifiable to speculate that this may explain some of the unusual clinical features of survivors with congenital heart disease. For instance, the large left ventricle in small or spontaneously closed ventricular septal defects and the HOCM-like response and disproportionate septal size which may occur with mild bicuspid aortic valve stenosis and with classic congenital aortic valve stenosis in the young, and which is a constant feature of the variant form of aortic valve stenosis with poorly formed lumpy aortic valves and also gross 'higgledy piggledy' changes throughout the aorta (Somerville and Ross, 1977), might be related to the presence of too much dysplastic myocardium. Could the presence of unusual amounts of dysplastic myocardium explain left ventricular dysfunction with secondary mitral cusp prolapse in simple atrial septal defect or the strange septal T inversion which can persist in adolescents with simple congenital heart disease? Perhaps of greater interest is that it might explain the development of subpulmonary obstruction in classic transposition of the great arteries (Somerville and Becú, 1977b) as well as the persistence of infundibular gradients after pulmonary valvotomy for severe pulmonary valve stenosis.

Corroborative evidence, but not proof, comes from the finding of extensive areas of myocardial dysplasia in the appropriate part of the heart in all these situations. We believe that the disturbed circulatory mechanics resulting from the structural lesions stimulates secondary changes in the form and function of the dysplastic muscle so that it in turn influences the mechanical disturbance. Once obstruction in a muscular outflow begins, turbulence occurs, fibrous tissue is laid down, and a vicious circle of effects upon the myocardium may be initiated which is only partly checked by removal of the fixed part of the obstruction. If the primary abnormality is really in the myocardium the clinical state even after good surgery may evolve unfavourably as is shown by the natural history of fixed supraaortic stenosis (Somerville and Montoyo, 1971; Somerville and Becú, 1977b). These clinical states share not only the pathological features but also many of the haemodynamic features of the diseases embraced by the term hypertrophic cardiomyopathy. How the dysplastic myocardium actually influences the electrocardiogram also needs clarification.

Aetiological factors

Myocardial dysplasia like the abnormal 'higgledy piggledy' pathology in the aorta with which it is commonly but not constantly associated results from several known different noxious agents which affect the fetus and its cardiovascular system. For instance, both are common in the hearts and vessels of children affected by rubella, and are constant in supra-aortic stenosis of varying causes including vitamin D or vitamin E intoxication, anticonvulsant and other drugs, familial, and even those where there is no obvious cause. Dysplasia or disorganised alignment in cardiovascular tissue probably is the result of incomplete 'healing' or development after intrauterine damage and is probably as non-
specific as scar tissue in skin which tells nothing about the original injury. If the concept is true that myocardial dysplasia is frequently present in congenital heart disease as part of diffuse congenital cardiovascular damage caused in utero, then it should also be found in other examples of fetal (or congenital) syndromes without obvious structural congenital heart disease. In fact, clinically manifest hypertrophic cardiomyopathy is frequent in Noonan’s syndrome (Ehlers et al., 1972), lentiginosis (Somerville and Bonham-Carter, 1972), Friedreich’s ataxia (Thorén, 1977), fetal alcohol syndrome (Löser et al., 1977), the children of diabetic mothers (Gutgesell et al., 1976), and other named syndromes (Stocker et al., 1977). It is predicted that the association will be described in more congenital syndromes.

Conclusions

When hypertrophic cardiomyopathy and congenital heart disease coexist the myocardial abnormality must be severe to be recognised. It is likely that the importance and incidence of the association has been underestimated because unaware pathologists and clinicians do not look for it. In few well-documented cases of the two conditions occurring together the structural congenital cardiac lesion would have had a relatively good prognosis if it had occurred in isolation. This allows time for the post-natal adaptive changes in the abnormal myocardium to occur and influence the clinical presentation. The finding of histological changes called myocardial ‘dysplasia’, which are indistinguishable from HOCM or ASH, is common in congenital heart defects of all types and may be associated with macroscopical ventricular myocardial abnormalities which cannot be explained by the mechanical disturbance. What determines whether myocardial dysplasia will influence the clinical picture is unknown but we believe it is related to the extent and distribution of abnormal muscle in the heart and the secondary factors which influence it. It is suggested that a number of unusual clinical features in congenital heart disease may be explained by the presence of, and the secondary effects on, excess myocardial dysplasia.

There is a close association between the finding of myocardial dysplasia and abnormal ‘higgledy piggledy’ changes in the aorta and major conducting arteries, which coexist in some congenital heart diseases, syndromes which manifest with arterial stenoses, and in isolated hypertrophic cardiomyopathy of various aetiologies. We believe that both histological abnormalities are non-specific and are a common end result of an attack on the fetal cardiovascular system.

There is more congenital abnormality in these hearts than the obvious hole, valve abnormality, or disorder of connections, and such hearts should be correctly diagnosed as ‘congenital cardiovascular disease’. Both myocardial and arterial disease may affect the survivors with both simple and complex cardiac malformations.

Understanding of this problem may also throw light on the mysterious group of diseases classified as ‘hypertrophic cardiomyopathy’ which the pathologist can diagnose with apparent certainty when the clinical and macroscopical features are obvious. Our studies suggest that the diagnostic myocardial dysplasia is common in congenital heart disease and may sometimes, depending on the intensity of one’s search, be associated with clinical myocardial dysfunction such as is found in hypertrophic cardiomyopathy.

Perhaps there is a parallel between the presence of myocardial dysplasia and that of malignant cells. Many hearts contain myocardial dysplasia, particularly those with structural congenital heart disease since it is a congenital disorder. Similarly, many people have malignant cells but it requires certain secondary factors, predispositions, and critical numbers for them to become a clinical problem. What makes myocardial dysplasia become clinical hypertrophic cardiomyopathy or influence dynamics in congenital heart disease requires more study. The preoccupation with the non-specific histological end point should now be redefined

References

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