Endomyocardial fibrosis in Africa

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Summary

Endomyocardial fibrosis (EMF) is a disease of the rain-forest belt in Africa. There is general agreement as to its pathology in the acute phase, but this is difficult to diagnose clinically. The aetiology is still unknown although there are reports which suggest that eosinophilic endomyocardial disease may be the cause. Further studies are needed to define EMF in its acute stage and find out how chronic EMF evolves. A longitudinal study on young people with eosinophilia and a comparative study of two villages, one in an endemic zone and the other in a zone where EMF is uncommon, will also be helpful in identifying its cause. The most promising form of treatment at present is surgical.

KEY WORDS: endomyocardial fibrosis, Africa.

Introduction

Since Bedford and Konstam reported the first cases of endomyocardial fibrosis (EMF) in 1946 among African soldiers who were mainly from West Africa and who had served in the Middle East during the second world war, there have been numerous reports of its clinical, pathological, haemodynamic and radiological features. The first part of this paper will therefore be devoted to a summary of what we know about this fascinating disease in Africa, while the latter part will try to identify areas in which our knowledge is deficient and where our research efforts should be directed.

Epidemiology. EMF occurs worldwide, but mainly in the tropical and sub-tropical areas. In Africa, it has been reported from Kenya, Tanzania, Mozambique, Gabon, Uganda, Ivory Coast, Ghana, Nigeria, Cameroons, Sudan, and Congo Brazzaville (O'Brien, 1954; Williams, Ball and Davies, 1954; Turner and Manson-Bahr, 1960; Parry and Abrahams, 1963; Connor et al., 1967; Shaper, 1968; Bertrand, 1979; Bijlisma, 1979). It is uncommon in Northern and Southern Africa.

EMF occurs mainly in the hot and humid coastal areas of Africa typified by Nigeria whose climatic zones can be divided into the hot and humid coastal area with its tropical forest vegetation, and the hot and dry North with its savannah vegetation (Fig. 1) (Okuwobi, 1968; Brockington and Edington, 1972; Ladipo, Froude and Parry, 1977; Ladipo, 1978).

Age and sex distribution. Like rheumatic heart disease, EMF predominates in children and young adults (Parry, 1964; Shaper, 1972; Bijlisma, 1976). A female preponderance (F/M ratio = 2/1) has been noted in Kampala (Connor et al., 1967; Shaper, 1972), but not in Ibadan where some workers have found no sex difference while others have found a male preponderance of 2 to 1 (Brockington and Edington, 1972; Parry, 1964).

Ethnic and class distribution. In areas where EMF is common, several workers have pointed out that there seems to be an ethnic disparity. In Nigeria, for example, Parry (1964) and Brockington (1974) found that most of the patients seen at Ibadan came from the Ijebu ethnic group in Western Nigeria, although recent studies have disputed this. Of 52 patients seen by Jaiyesimi (personal communication) at the Paediatrics Cardiac Unit, 46 were Yorubas and 6 Ibos. There was no patient from the Hausa or Fulani stock who live in the Northern part of Nigeria. The ethnic distribution of the 46 Yoruba patients was similar to the overall ethnic distribution of children who attended the paediatric cardiac and general clinics of the University College Hospital (UCH), Nigeria, during the period of study. It does not indicate a predisposition to EMF amongst the Ijebu (Brockington, 1974).

In Uganda, however, Shaper, Hutt and Coles (1968) have shown a preponderance of EMF among poor migrant labourers from Ruanda and Burundi. It is also common among the people from Ankole in South-West Uganda, but less common among the Ganda people who are indigenous to the Kampala region of Uganda. Malaria transmission is common at all seasons in areas where Ganda people live, but absent or seasonal in Ruanda and Burundi. Thus,
malaria was suspected as important in the aetiology of EMF. The migrant labourers from Ruanda and Burundi are, however, poor, while the indigenous Ganda tribe are relatively affluent. Similarly, EMF is rare in the middle and upper classes and predominates in the lower socio-economic class. It is therefore probable that malaria, if it plays any part at all in the aetiology of EMF, is not the only factor.

Finally, EMF has been described in Europeans previously resident in Africa (Brockington, Olsen and Goodwin, 1967), as well as in other Caucasians and Asiatics who have never lived in Africa (Libanoff and McMahon, 1976; Chew et al., 1977; Hess et al., 1978).

Pathology. The macroscopic and microscopic features of EMF are well-described (Davies, 1948; Davies and Ball, 1955; Edington and Gilles, 1976), and a detailed review will not be given here. Briefly, the disease, as the name suggests, is characterised by scarring of the endocardium and the inner third of the myocardium. The fibrosis often affects the inflow tract of either or both ventricles and sometimes the atria (Edington and Gilles, 1976; Ball, Williams and Davies, 1954). It usually spares the outflow tract. The fibrosis starts at the apex of the affected ventricle and extends to involve the papillary muscles and chordae tendinae. Involvement of the latter structures results in one of the valve leaflets (usually the posterior valve leaflet) being perpetually held open and consequently, severe atrioventricular incompetence. The distribution of the fibrosis in the ventricle tends to vary and five types are recognised (Shaper et al., 1968; Hutt, 1970). In type 1, the fibrosis affects only the apex. In type 2, it affects the apex and extends to involve the valvular area. In type 3, EMF affects only the valvular region while in type 4 there are isolated lesions in the apex and the valvular region. In type 5, the lesions are patchy, affecting areas other than the apex or valves. Obviously only types 2, 3 and 4 will present with atrioventricular incompetence while types 1 and 5 may not show any clinical manifestation and be missed. Fibrosis, if extensive, will cause a reduction in ventricular cavity and diastolic filling, and at the same time impair systolic contraction, thus reducing stroke volume and cardiac output.

All the above, however, are the changes seen in chronic cases. What of the acute cases? Shaper (1974) states that 'in the more acute cases of EMF, the endocardial lesions are covered with a soft, spongy,
greyish-green layer of thrombus... There seems to be general agreement regarding pathogenesis. An initial acute endomyocardial lesion with overlying fibrinous deposits proceeds to lesions with adherent thrombi, followed by the incorporation of these thrombi into a fibroed and contracted ventricle.

Clinical features. The clinical presentation of EMF depends on the chamber involved, the location of the fibrotic lesion and its severity. However, the classic descriptions are those of severe, advanced EMF.

Right ventricular EMF presents with 3 obvious features: a very high venous pressure with a dominant systolic wave indicative of tricuspid regurgitation, massive abdominal distension from gross ascites and liver enlargement and minimal or no ankle oedema (Falase, Kolawole and Lagundoye, 1976). On auscultation, the most distinct sign is an early third sound. The murmur of tricuspid regurgitation is often absent because the right atrium and right ventricle virtually constitute one chamber and the right ventricle is too weak to generate audible vibrations. Some of the patients have extracardiac manifestations such as central cyanosis caused by the huge heart, clubbing of the fingers and toes from the cyanosis, proptosis from chronic tricuspid regurgitation, peri orbital hyper pigmentation, which is a residue of small haemorrhages from congested peri orbital veins, oral and gingival hyper pigmentation of unknown cause, parotid swelling from cardiac cirrhosis, growth retardation and finally retardation of sexual maturation. Furthermore, many of them suffer from psycho-social problems as a result of their disease (Jaiyesimi and Falase, 1976).

The chest X-ray shows a globular heart from cardiac enlargement and often massive pericardial effusion. Right ventricular endocardial calcification may sometimes be present, the lung fields are usually oligaeic because of decreased output from the right ventricle and, consequently, decreased lung perfusion. The electrocardiogram usually shows low voltage complexes because of pericardial effusion, some of the patients are in atrial fibrillation while many of them show a QR pattern with ST depression in leads V1, V2, and V3. M-mode echocardiography usually shows paradoxical septal motion, reduced right ventricular cavity, thickening of the anterior ventricular wall and infundibular dilatation (George et al., 1982).

The signs of left ventricular EMF are those of mitral incompetence and left ventricular failure. Pulmonary oedema occurs in the early stages, and later, as the pulmonary vascular resistance rises, signs of pulmonary hypertension are found (Somers and Fowler, 1968). The electrocardiogram usually shows left ventricular hypertrophy and T wave inversion in the lateral leads. The chest X-ray may be normal and only the presence of endocardial calcification may suggest the diagnosis. M-mode echocardiography usually shows thickening of the posterior ventricular wall, increased left atrial dimension and, in a few instances, abnormal echoes in the sub mitral region.

In both right and left ventricular EMF, the definitive diagnosis is made on angiography. Pressure tracings are similar in the right atrium and the right ventricle, and they show a restrictive pattern (Goodwin, 1983).

The early manifestation of EMF. The above description of the typical changes seen in chronic, advanced cases. What then are the clinical features of the early cases? This is very important as the aetiological factor(s) in EMF might not be operative or discernible by the time a patient is in the chronic stage.

Parry and Abrahams (1966) described what they considered to be the initial illness of EMF. They sought clues to the beginning of EMF from patients with proven EMF and found that some of them had a past history of fever, swelling of the face and body, rapidly progressive breathlessness and clinical evidence of carditis with little or no atrioventricular valvular incompetence. It has however, been difficult to substantiate this claim. As Parry (1976) later admitted, febrile disorders are very common in the tropics, and nobody has, to my knowledge, observed the transition from a febrile illness described above, to chronic EMF.

Of late, several workers have suggested that EMF begins with a hypereosinophilic illness like Loeffler's endomyocardial disease. They postulate that an acute hypereosinophilic disorder associated with pancytopenia is the initial illness while EMF is the end-stage disease (Olsen and Spry, 1979). This concept is examined below. Acute illness due to hypereosinophilia is very rare at Ibadan and none of us has clinically observed this transition from acute hypereosinophilic disease to chronic EMF. Thus, as at the moment, the clinical features of the acute stage of EMF are unknown.

Aetiology

In spite of the considerable literature on EMF, its aetiology remains unknown.

Nutritional factors. EMF is a disease of developing countries in which poverty and malnutrition are rampant and EMF predominantly affects poor people. However, EMF has occurred in well-nourished Caucasians resident in tropical Africa. Furthermore, malnutrition will not explain the confinement of EMF to the rain-forest areas of Africa nor the differences among ethnic groups in the same country.
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**Serotonin.** Excess of serotonin (5-hydroxytryptamine) in the blood stream, as in carcinoid syndrome, is known to produce a cardiac lesion which was thought to resemble EMF (Ball, 1957). Serotonin is present in large quantities in plantains and bananas (West, 1958; Marshall, 1959) which are consumed in large quantities in communities where EMF is common. Arnott (1959) therefore suggested that EMF might be due to excessive consumption of plantains. This view was further reinforced by the work of McKinney and Crawford (1965) who produced cardiac lesions in guinea-pigs fed on a plantain diet.

However, on epidemiological grounds, this theory could not be substantiated, for EMF is rare in some communities, such as the West Indian, which consume large quantities of plantains and bananas. Furthermore, Williams (1967) has found that there was no correlation between the geographical distribution of EMF and the plantain-eating habits of the African population. Experimental studies by Antia, Talbert and Paplanus (1968) and measurement of serotonin levels under various conditions by Ojo (1970) have also conclusively shown that serotonin has no part to play in the aetiology of EMF. Finally, the lesions of the carcinoid syndrome are entirely different from those of EMF.

**Vitamin E deficiency.** Vitamin E deficiency in some malnourished animals is known to produce lesions which resemble EMF (Lee, King and Vischer, 1960). The role of vitamin E in man is to prevent oxidation of tissue lipids. Its deficiency therefore leads to auto-oxidation of unsaturated lipids with deposition of ceroid bodies in the tissues (Pappenheimer and Vitor, 1946). These ceroid bodies later become fibrosed and in the endocardium this leads to endocardial fibrosis. We therefore studied the vitamin E status of 14 patients with EMF and 8 patients with cardiac failure from other causes using the peroxidase haemolysis test and found that none of the patients was vitamin E deficient (Jaiyesimi, Ojo and Falase, 1978). Our results, however, could not be regarded as conclusive since we studied patients with advanced EMF when the aetiological factor may not be operative.

**Obstruction of cardiac lymphatics.** Obstruction to cardiac lymphatics has been suggested as the aetiological factor by Miller, Pick and Katz (1963). They produced surgical blockage of cardiac lymphatics in 73 dogs and found ventricular subendocardial haemorrhages, endocardial thickening due to increase in fibrous and elastic tissues, and greyish white endocardial opacification in many of the animals. These findings have, however, not been confirmed (Antia et al. 1968; Adebonojo, personal communications).

**Rheumatic heart disease (RHD) and EMF.** RHD and EMF have some similarities with a similar age and sex distribution, and a peculiar tribal and geographical distribution in East Africa, and both appear to be disorders of cardiac connective tissue based on a hypersensitivity mechanism. Moreover, they have been found to coexist in some patients (Nwokolo, 1955; Abrahams and Brigden, 1961). However, the pathological lesions are strikingly dissimilar and there are many communities in which RHD is common but EMF rare.

**EMF and dilated cardiomyopathy.** Edington and Jackson (1963) suggested that dilated cardiomyopathy was an early form of EMF. Since then, there has been no study confirming that such an evolution could occur. If dilated cardiomyopathy progresses to EMF, the latter would be expected to occur in the older age group and dilated cardiomyopathy in the younger, but the reverse is the case.

**Immunological aspects.** In Kampala, Uganda, bound IgG has been demonstrated in the sarcolemmal and sub-sarcolemmal sites in myofibres and, to a much lesser extent, in the endocardium of patients with EMF (Van der Geld et al., 1966). This finding is, however, not specific for EMF because similar deposits have been found in rheumatic hearts (Kaplan, 1964) and in patients with dilated cardiomyopathy (Sanders, 1963).

Patients with EMF have also been shown to have antibodies to cardiac tissues but the presence is not specific for EMF. A progressive increase in frequency of such heart antibodies with increasing titres of malarial antibody has, however, been found by Shaper (1974), with a significant relationship between high titres of malaria antibody and high levels of IgM. Furthermore, those with high levels of IgM and malarial antibody also had a high frequency of heart antibodies, thyroid antibodies, gastric parietal-cell antibodies and rheumatoid factor. So far there has been no positive proof of the involvement of this 'tropical immunological' syndrome in EMF and later studies by Carlisle et al. (1972) and Andy and Olusi (1981) have not shown any significant role for immunoglobulins in the aetiology of EMF.

**Parasitic infections, eosinophilia and EMF.** There is now a wealth of evidence which shows that Loefffer's endocarditis produces endomyocardial disease which in its later stages resembles EMF (Brockington and Olsen, 1973; Brockington, 1974; Olsen and Spry, 1979; Olsen, 1983). The only difference between the two diseases is that hypereosinophilia is common in Loefffer's endomyocardial disease but is lacking in EMF. Olsen and Spry (1979) have, however, pointed out that eosinophilia may be absent at the late stage.
of Loeffler's endomyocardial disease while eosinophilia may occur in patients with EMF, though not to a considerable extent. The damage to the endomyocardium is caused by the eosinophils themselves.

Eosinophilia is very common among people in the tropics, but hypereosinophilia with endomyocardial disease i.e. Loeffler's endocarditis, is distinctly rare and I doubt if these cases are being missed. If Loeffler's endomyocardial disease is the acute phase of EMF, which is a common disease, I would expect that we would be seeing more cases of the former disease than at present. Secondly, eosinophilia also occurs commonly in areas where EMF is rare and it becomes difficult to explain the geographical distribution of EMF if Loeffler's endomyocardial disease is the precursor of EMF.

Thirdly, we have investigated a few patients with symptomless hypereosinophilia, mainly parasitic, but one due to Hodgkin's disease and found no evidence of EMF. In the series reported recently by Andy, Bishara and Soyinka (1981), only 29.5% of the patients with hypereosinophilia had EMF, so that clearly not all cases of hypereosinophilia develop endomyocardial disease.

There may however be agents which induce hypereosinophilia in the rain-forest regions of the tropics where EMF commonly exists. Filariasis has been investigated as a possible inducer of such hypereosinophilia. Ive et al. (1967) found evidence of filariasis in between 64 and 83% of EMF patients but only 36 to 49% of controls. They therefore suggested that Loa-loa might be the pathogen. However, Carlisle et al. (1972) could not confirm this finding and found that the prevalence of Loa-loa precipitin antibodies in patients with EMF was not different from patients with organic heart disease. Brockington (1974) has argued that the geographical distributions of EMF and Loa-loa are dissimilar, but this conclusion was based on the assumption that EMF in Western Nigeria was particularly common among the Ijebus. As pointed out earlier this has been shown not to be the case.

Andy et al. (1981) found evidence of filariasis in EMF patients with hypereosinophilia. While it is possible that filariasis was the inducer of hypereosinophilia and EMF in their series, it is also possible that filariasis was a coincidental infection in patients who were already in advanced stages of EMF.

Jaiyesimi, Onadeko and Antia (1979) recently reported a syndrome of EMF, schisostomiasis and dermatosis due to Schistosoma mansoni in 4 Nigerian children. Liver biopsy revealed cirrhosis in one patient and hepatic granulomata in the remaining 3. Osunkoya et al. (1972) had earlier demonstrated

Fig. 2. The plain chest X-ray of a 14-year-old girl with severe EMF.
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Fig. 3. Right ventricular angiogram of the same patient as in Fig. 2, showing severe tricuspid regurgitation, a dilated right atrium, an almost non-existent right ventricle and a large pericardial effusion.

hepatic granulomata in patients with EMF. Though, as Jaiyesimi et al. (1979) concluded, the blood eosinophilia secondary to the *S. mansoni* infection damaged the endocardium, it is also possible that *S. mansoni* was a coincidental infection.

Treatment. Medical treatment is often unsatisfactory. Surgical management is therefore the treatment of choice (Dubost, 1983). Reports from the Ivory Coast showed that endocardial resection with or without atrioventricular valve replacement produced good results. Of the 25 patients operated on so far, 6 died while the rest were significantly improved (Coulibaly et al. 1981).

Facilities for open heart surgery are, however, not available in most parts of Africa. Surgical management, therefore, is mainly for relief of those complications which are responsible for a poor response to medical therapy. These include pericardectomy and valved pericardio-peritoneal shunts for relief of massive and recurrent pericardial effusion (Adebonojo and Jaiyesimi, 1977), and recurrent abdominal paracentesis to relieve the massive ascites and make the patients acceptable to the society. We have created a right atrium to pulmonary artery shunt in two patients who failed to respond to medical management and pericardial stripping (Figs. 2,3 and 4) and found that they improved considerably. This operation was meant to increase blood flow to the lungs. Evaluation of this operation will have to await a larger series.

Conclusions—future research

From the foregoing, it is apparent that the general distribution, pathology and clinical features of chronic EMF in Africa are well-established. The clinical features of the early phase of the disease and its aetiology, however, continue to elude us. Yet, it is during the acute phase that we have the best chance of detecting the aetiological factor(s). The association of eosinophilic endomyocardial disease with chronic EMF is promising, but a number of questions still remain to be answered.

The fact that EMF occurs only in the rain-forest belt of Africa and that it affects both indigenous and non-indigenous inhabitants suggests that it is an environmental disease. Our suspicion is that it is caused by an infective agent, transmitted to a susceptible individual by a vector which is confined to the tropical rain-forest area of Africa. Whether this agent induces EMF by causing hypereosinophilia or
whether it does this on its own is not clear. What makes an individual susceptible is also not certain.

However, it is clear that our efforts should now be directed at defining the clinical features of EMF in its early stages and finding out how its chronic form evolves. If indeed, eosinophilia is the cause of EMF, there is a need for a longitudinal study on young people with eosinophilia for confirmation. Furthermore, a comprehensive, comparative study of two villages, one in an endemic zone and the other in a zone where EMF is uncommon, would be fruitful.

These studies in my opinion would offer us the best hope of discovering the aetiology of this disabling disease, thus enabling us to apply appropriate preventive measures.

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