Thalassaemia major and the heart

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Introduction

Disorders of haemoglobin synthesis are the commonest monogenetic disorders worldwide. When first described, thalassaemia was universally fatal in childhood, but after the adoption of regular blood transfusion survival until early teenage and adulthood was to be expected. At that stage in the life of these affected individuals organ failure followed, due to accumulated iron, for which the human has no excretory capacity. Principal amongst the tissues affected by iron overload is the heart and even to the present day, heart disease accounts for the overwhelming majority of premature deaths in this population. Managing transfusion derived iron overload was the next hurdle for clinicians and the families of the patients. For nearly four decades the only available treatment was the demanding regime of parenteral chelation therapy, required on a daily basis, to achieve growth, development and survival with limited or no organ damage. Despite the adoption of these treatment strategies the outlook for thalassaemia patients remained poor, with a 30% to 40% mortality occurring between late teenage and 30 years of age, even in well organised health care systems, such as in the UK, where regular transfusion and desferrioxamine treatment were readily available. This dreadful early mortality, largely as a consequence of myocardial iron overload, (1,2) is now improving so that in the UK and other developed nations, heart failure in thalassaemic patients has become uncommon and premature death a much rarer tragedy. This editorial reviews, from a personal viewpoint of a cardiologist involved in the care of these patients for the last 20 years, the progress in the management of the cardiovascular complications of thalassaemia major (TM), which has followed better techniques of identifying those thalassaemic individuals at greatest risk, improved chelation strategies making best use of the three

chelating agents that are now available and improved co-ordinated holistic treatment strategies, derived from a better understanding of this complicated disease state.

The thalassaemias

The first clinical descriptions of thalassaemia as a new disease entity were published in 1925 independently by Cooley in the United States and by Rietti, Greppi and Michelli in Italy. (3) The term thalassaemia was coined by Whipple in 1932 after performing the first autopsies in thalassaemic patients. Whipple wished to link the geographical origins of the patients he examined, the Mediterranean, with the blood disorder. This name was finally shortened to thalassaemia, a term that has persisted to this day. Over many decades, the underlying genetic abnormalities resulting in thalassaemia have been identified. (3)

Although the clinical manifestations of iron overload do not usually appear until the second decade of life, evidence from liver biopsies indicate that the damaging effects of iron accumulate much earlier than this. After approximately one year of transfusions, iron begins to be deposited in parenchymal tissues and may cause toxicity. (4) Where the heart is concerned the data support the impression that significant myocardial iron overload is seen after the age of 10 yr, (5) but sporadic reports exist of patients as young as 7 yr having iron in the heart. (6)

Iron toxicity

Iron is a necessary constituent for cellular function, but it is rarely found unbound due to its highly reactive nature and ability to generate or catalyse the formation of toxic free radicals via the rapid Fenton reaction. (7) Iron is transported bound to the plasma protein transferrin and is taken up by cells via specific cell surface receptors. The regulation of iron metabolism is complex and incompletely understood. (8) In the presence of excess iron the carrying capacity of transferrin is exceeded and free non-transferrin bound iron (NTBI) is found in plasma. NTBI is taken up rapidly by myocytes, liver and other tissues. Uptake of iron into myocytes is complex and incompletely described, although the divalent metal transporter 1 (DMT1) and L-type calcium channels appear to be involved. (9,10) The uptake of iron in heart cells may be influenced by other genetic factors, one such being glutathione S-transferase-M1 (GSTM1) gene deletion, which has been associated with increased myocardial iron content. (11,12)

Iron once within the cell is bound to ferritin and transported to lysosomes for degradation and long-term storage. (13) If storage capacity is exceeded, free intracellular iron is able to be highly reactive (7) and cause multiple toxic cellular effects, including, impaired Na-K-ATPase activity, increased lysosomal fragility and impaired mitochondrial respiratory chain activity (14,15,16) and the potential to worsen any

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A full version of this article, including a complete list of references will be published in Heart and will be available for viewing at "Heart.BMJ.com"

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Thalassemia Reports 2013; 3(s1):e8

doi:10.4081/thal.2013.s1.e8

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Parts of this work were presented at the "3rd Pan-European Conference on Haemoglobinopathies and Rare Anaemias", Limassol (Cyprus), 24-26 October 2012.

ischaemia induced reperfusion injury. (17,18) The eventual consequence is heart failure. (19)

The relatively mild degree of fibrosis in most autopsy studies suggests that even when advanced, the cardiomyopathy has the potential to be reversible. (20,21,22) Thus the accumulation of iron within myocytes is a problem of storage, only when this capacity is exceeded, or the cell subjected to stress do the harmful effects of iron become manifest, raising the possibility that removal of excess iron deposits has the potential to restore the cell to normality, an observation made clinically on numerous occasions. (23,24,25)

Clinical cardiovascular manifestations of thalassaemia

The clinical presentation of thalassaemia varies greatly between individuals and at different ages. Infancy and childhood are dominated by the effects of anaemia a high cardiac output state and secondary spleen enlargement, but, as the transfused child ages, skeletal and endocrine effects appear, to be followed much later by the combined effects of the anaemia, erythroid marrow expansion, and the increasing effects of iron overload. As a consequence of the widespread iron deposition in the body, serious clinical complications arise by the involvement of the heart, liver and endocrine glands. Although myocyte dysfunction due to iron overload is the single most important cause of cardiac complications in thalassaemia, previously there was a significant incidence of myocarditis (4% of a sample population), (26) although both conditions are much less common now, presumably due to improved treatment. (27)

The baseline haemodynamic state associated with thalassaemia affects the clinical assessment of patients and can complicate the diagnosis of ventricular dysfunction. Knowledge of these characteristics is important and informs the appropriate use of standard treatments of ventricular failure.

Despite regular transfusion, patients with thalassaemia major are maintained with a mild chronic anemia (characteristically averaging 10 g/dl) and have a raised cardiac output. (28,29) Additionally, there are physiological adaptations to this state, including increased left ventricular dimensions, when compared to age matched peer groups. (29) Systolic blood pressures are lower due to a reduced peripheral vascular resistance. (30) This *hyperdynamic* circulation is also evident in the higher ranges of ejection fraction seen in TM without iron overload, (29) (lower limit EF in this population is >63% EF. (31,32) Endothelial function is adversely affected by iron overload, with worsening in parameters of flow-mediated dilatation, which improve towards normal with iron chelation therapy. (33) Iron overload appears to accelerate age-related increases in vascular stiffness (34) and aortic and peripheral vascular compliance worsens with iron overload and with age. (35) These complex vascular effects have the potential to influence cardiac function and adaptation to stress. (36)

Cardiac iron overload is therefore rarely found in isolation, but is part of complex multisystem disease, even in a monogenetic disorder such as thalassaemia.

Iron overload and the heart

Heart failure

Once clinical evidence of cardiac failure is apparent in iron overloaded hearts the prognosis is poor, with mean survivals in the region of 3 months in historical reports (37) and remaining poor in more

recent reports, where longer-term survival after heart failure in adult patients (ages 24±5 years) was only 48%. (38) Our own experience is that the acute mortality of overt severe cardiac failure is high, approximating 50%, but, if intensive chelation is undertaken successfully, subsequent survival is good with normalisation of ventricular function to be expected, although clearance of cardiac iron lags behind improvements in systolic function, (23) with a high risk of relapse occurring if intensive chelation therapy is prematurely discontinued. (39) The clinical imperative is therefore to identify iron-overloaded hearts early, before severe myocyte failure occurs.

Identifying thalassaemia patients at risk of heart failure

In the past this was difficult. The non-specific nature of symptoms attributable to myocardial dysfunction reduces their reliability as discriminators between high and low risk patients. The chronic anaemia alone may account for much exercise limitation, although many patients with thalassaemia will be able to detect a progressive deterioration across time, which cannot be accounted for by their haemoglobin levels. The at-risk thalassaemic population could be found amongst the individuals, aged from teenage to early twenties, often with a history of difficulty with compliance to the DFO infusion regime. (40) Low risk individuals would tend to have long-term average ferritin levels under 1,500 with the absence of other organ involvement. (41) These patients were usually non-diabetic, with normal secondary sexual development, normal growth and endocrine function. Unfortunately, within any clinical service dealing with thalassaemia tragic exceptions occurred all too frequently. Patients who ostensibly were expected to be at low risk were subject to rapid decompensation. In the UK where the thalassaemia community is relatively small and close-knit, such unexpected deaths of young people had enormous effects on the morale and motivation of the survivors, further undermining compliance with a very demanding, often painful and socially debilitating form of treatment that DFO infusions represent.

Historically, the most accurate assessment of total iron burden relied upon quantitative iron measurement in liver biopsies. (42) However, the relationship between liver iron content and heart iron content is not constant. Finding a clear liver biopsy failed on occasion to identify some individuals, who were at great risk due to high heart iron content and the alternative scenario of low heart iron content with a high liver iron was also encountered. Myocardial biopsy had been used to risk stratify patients, (42) but its invasive nature and a concern over potential sampling errors precluded its routine use. (43)

The development of an MRI based non-invasive method to measure tissue iron accumulation (44) establishing the T2* parameter, transformed the ability to adequately risk stratify the thalassaemic patient population. Cardiac T2* has been shown from a study of autopsy hearts to have a predictable relationship to physical iron content. (45) Increasing iron content, as shown by low T2* is associated with increasingly impaired ventricular function. (46,47) The T2* also responds to increased chelation treatment by showing a progressive rise towards normality associated with a dissociated, faster, improvement in ventricular function. (23,33) A prospective follow-up of more than 600 UK patients revealed that a T2* <6 ms conferred a 47% chance of developing heart failure within one year and 98% of patients with diagnosed heart failure had a T2* <10 ms. (48) There was a demonstrable *dose-response*, where higher T2* values were associated with decreasing risks of heart failure.

Within the thalassaemia population there is a group (approximately 40%) with normal LV function by conventional testing (EF), but severe iron loading, demonstrated by a low T2* (<10 ms). (47) These individuals pose a high risk of developing cardiac complications. These patients, before the advent of MR T2* measurements, went undetected and were not prescribed the intensified treatment regimes known to improve cardiac outcomes.

As a result, some have postulated that recent improvements in life expectancy for thalassemia major patients in the UK and elsewhere, (2) can be explained by the increasing availability of cardiac MRI and earlier escalation of therapy. (49)

Arrhythmia and heart conduction abnormalities

Iron overloaded hearts are susceptible to arrhythmia, occurring in 50% of patients from historical series of TM patients not receiving chelation. (50) It is not surprising therefore that palpitations are a relatively frequent complaint, as they are in any general cardiology service. They occasionally are due to life-threatening ventricular tachycardia (VT) (<1%), (48) but this is usually in grossly iron-overloaded hearts with established ventricular impairment. Atrial fibrillation is fairly common with a 12% incidence within a year in the prospective UK study (48) but a much lower incidence reported for a large cohort in Italy. (31) AF was previously associated with the risk of impending cardiac failure and was greatly feared by TM patients, who were aware of it as a harbinger of impending heart failure and likely mortality.

The demographic characteristic of AF appears to be changing in our clinics. A recent survey revealed a 9 % prevalence of AF and 34% incidence of documented AF or paroxysmal AF within the last 12 months amongst a cohort of TM patients of mean age 38 years, with good LV function and normal T2* values (unpublished observations, M Walker). In this ageing group, none of whom had significant current myocardial iron loading, the AF appeared to represent the very late manifestation of an historical cardiac iron overload.

The problem facing the clinician is differentiating between sinister arrhythmias and the more common benign palpitations experienced by a young population, often anxious, who have first-hand experience of the outcomes of some of their less fortunate peers. Having a quantitative estimate of cardiac iron content, by T2*, and current knowledge of ventricular function is essential in making this distinction.

Conduction disturbance and complete heart block (CHB) occurred in 40% of 16 to 20 yr old TM patients who did not receive any chelation in an early series. (50) In current practice heart block is rare. When encountered, CHB may respond to intensive chelation therapy and removal of myocardial iron, but the rate of progress is so slow that in the intervening period there will be a need to consider the use of a permanent pacemaker. In view of the essential nature of MR scanning in the continued assessment of TM patients, any devices used must be MR compatible.

Treatment of myocardial iron overload

The mainstay of treatment for iron overload remains the administration of desferoxamine (DFO), using prolonged subcutaneous or intravenous infusions. The introduction of DFO in the 1960s had a profound effect on mortality in TM. Although not specifically documented this was undoubtedly dominated by a reduction in cardiac mortality.

Patients at high risk of complications, or those with established evidence of cardiac dysfunction need an intensive regime of treatment, which usually means constant 24 hour infusions for 7 days per week. These can be achieved using sub-cutaneous infusions, but more often, particularly in the more severely ill patients, constant intra-venous infusions are more effective. Chronic indwelling venous catheters or sub-cutaneous ports (Port-a-Cath) are preferable, since the chronic intra-venous treatment may have to be continued for years to achieve effective iron removal from the tissues. Focusing the most intensive regimes on those at greatest risk is an important clinical aim. To this end, aggressive treatment regimes can easily be justified in patients with established myocardial dysfunction or symptoms. With the advent

of MRI T2* encouraging such treatment in patients with high heart iron content, before there is any evidence ventricular impairment is appropriate.

Deferoxamine is not only difficult to use, but also remains very expensive and a proportion of patients develop allergies. An oral iron chelator, deferiprone (Ferriprox, ApoPharma; L1) has been available for some years. (51) Initially heralded as a great advance, it subsequently attracted adverse publicity from some quarters. (52) This negative data has been contrasted with positive results in several other studies, both retrospective (53,54) and prospective. (33,47) Deferiprone may have an advantage over DFO in its ability to enter the cell (55) and remove accumulated iron from the cytosol and probably from mitochondria. Combining treatment with DFO and deferiprone may have a particular advantage. The most recent addition to the chelation therapeutic field is another oral agent desferasirox, (Exjade; ICL370) (DFX), which has been licensed for use by the FDA and the European regulatory authorities and its clinical role is becoming more clearly defined. (56,57)

Specific cardiological care

The essence of treatment of cardiac disease should be aggressive chelation therapy to rapidly counteract iron toxicity and progressively remove excessive iron deposits. (39,58) In recent years, there has been a consistent trend to treat patients with thalassaemia who have mild ventricular dysfunction with agents known to improve myocardial function in other forms of cardiomyopathy, such as ACE inhibitors, angiotensin receptor blockers and beta-blockers. These drugs are established forms of treatment in cardiomyopathy, and while their extension to heart failure in thalassaemia remains conjectural, it is widely applied in clinical practice. Low blood pressure limits the use of these drugs in the TM population, as it does the use of beta-blockers for the treatment of symptomatic arrhythmia.

A special caution needs to be raised for the use of loop diuretics in the decompensated TM patient. Whilst symptomatic benefit may follow their use for pulmonary congestion or signs of right-sided heart failure, the tendency for thalassaemia patients to have low blood pressure plus a restrictive physiology, can precipitate a sudden fall in cardiac output and induce pre-renal failure.

Summary

For most cardiologists, thalassaemia major and the cardiomyopathy of iron overload remain infrequently observed clinical curiosities. Worldwide these are important problems, where, unusually, there exists a preventable form of cardiomyopathy, which, poorly managed, has the capacity to radically shorten lives and be the cause of distressing morbidity. In many countries, mostly in the developed nations, there has been a dramatic reduction in the death rate associated with the cardiovascular consequences of the condition. These improvements have arisen from clinical research and the more careful application of existing technologies and treatments to the individuals at highest risk, rather than to radical new discoveries.

TM also affords the opportunity to understand myocardial adaptive processes. This is a unique group of patients with a single cause for cardiac failure, which develops with an incidence of 3-5% per year even in those well-chelated adults with thalassaemia. Many of the mutations causing α -thalassaemia have been identified, and some of the reasons behind the very variable phenotypic expression of this monogenetic disorder are being unraveled. More uncertainties exist than answers, serving as a caution to the optimistic view that knowing the gene defect can

easily predict phenotype and then translate into clinical practice. Managing these patients optimally will still require careful clinical observation, measurement and well-planned trials of new therapies.

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