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## **The Heart and Thalassaemia an Update for UKTS 2012**

### **Introduction**

The thalassaemias were once diseases limited to childhood but, with the development of good clinical care, there has followed a remarkable improvement in outlook for affected individuals, the world over. Regular transfusions with good quality blood products and co-ordinated multidisciplinary medical care mean that thalassaemic patients now can now look forward to reaching adulthood and beyond. Thus the nature of the clinical problems faced by the thalassaemic community and their physicians are changing.

The initial challenge was the recognition of the place of regular blood transfusion and the progressive development of better systems to deliver high quality blood products in good time and with the least possible interruption of normal life. However with the need for regular blood transfusion comes the complication of tissue iron overload as the human body has no system to excrete the iron liberated from red blood cells that are destroyed. Intriguingly, even those individuals with the milder forms of thalassaemia, where transfusion is not undertaken or only required much later in life, have evidence of iron accumulation. This is through the mechanism of inappropriate intestinal iron absorption that affects thalassaemia patients.

## **Iron and the heart**

Iron accumulation is not evenly distributed through the body, but preferentially accumulates in certain tissues, such as the liver, certain regions of the brain, the pancreas and the heart. In the early experience of thalassaemia treatment with blood transfusion it became clear, that without adequate chelation treatment to remove iron, changes in heart function begin to appear from late teenage onward. The electrical conduction system, that controls the heartbeat and the strength of the heart muscle contraction become affected. Iron is an essential component in cellular processes and life cannot exist without it. The paradox is that in excess it becomes capable of generating very toxic compounds within cells, causing damage to the cell membranes and to the energy producing components, the mitochondria. Evolution has produced very effective mechanisms of packaging iron within cells, in forms that are safe. It is when these safe storage mechanisms are overwhelmed that damage is caused. Where the individual is concerned, even in the situation of very significant iron overload in the heart there may be few clues that any problem exists until a life-threatening crisis is precipitated, usually, but not always by an infection. This may not be an infection specifically involving the heart, but the mere presence of an acute illness uncovers a defect in heart function, where it cannot increase its output to fight the illness. The situations where heart muscles fail to contract normally are termed cardiomyopathies (cardio=heart; myo=muscle; pathy=sick).

## **Heart Failure**

When the heart cannot cope with the demands placed upon it the clinical syndrome of "heart failure" is present. For the individual concerned, the first signs of incipient heart failure may be subtle. The capacity to exert may decrease, breathlessness, firstly with exertion, but in more severe situations, even at rest are prominent symptoms. Chest pain is not usually a feature, but as the condition progresses there tends to be accumulation of fluid, in the ankles, in the abdomen and in the lungs. At this time other signs that the heart is not coping begin to appear, such as heart rhythm disorders and further reduction in blood pressure, which may be felt as faintness. However none of these symptoms are unique to heart failure and the clinician needs to undertake investigations to establish the precise cause of the problem and its severity. The ultra-sound examination of the heart, the echocardiogram, is a fundamental tool for this assessment. It must be emphasized that heart failure is now uncommon in thalassaemia. Once it is present, with the signs and symptoms noted above, the situation is advanced and intensive treatment, including intravenous DFO for 24 hr per day, 7 days per week is life saving; other chelation agents may also be introduced at this time to support and enhance

chelation effectiveness. The cardiologists at this time will also introduce other medications known to help failing heart muscle cells, these might include diuretics to help with fluid overload, beta-blockers to stabilize the heart rhythm and ACE inhibitors to support heart muscle function. Despite the life threatening nature of severe heart failure, in the context of thalassaemia it has the remarkable and unusual capacity of being potentially completely reversible, in this case by iron chelation therapy. There are few other conditions in cardiac medicine where hearts so severely compromised can be treated so successfully to restore not only function, but also years of normal life.

### **Identifying those at risk**

In managing patients with thalassaemia the imperative is to identify iron-overloaded hearts early, before severe heart failure has a chance to occur. In the past this has been difficult, long term ferritin values provide clues to risk, but when used alone failed to identify seriously affected individuals. The development of the magnetic resonance imaging parameter, named the T2\* (cMR T2\*) provided a non-invasive method to measure tissue iron accumulation and has transformed our ability to adequately risk stratify the thalassaemic patient population. The T2\* falls as the amount of iron in the tissue increases. A value of greater than 20 ms for T2\* confers a very low risk of developing significant heart complications (with the exception of atrial fibrillation, see below). Between 10 to 20 ms the risk of heart failure developing is significantly increased but it is when the T2\* falls below 6 ms that the chances of going into heart failure within one year approximate to a 50% risk. The cMR T2\* technique has been applied to liver iron accumulation, but it has been found to potentially underestimate liver iron content, so that most physicians prefer to use a commercially available specific cMR technique to assess liver iron (the Ferriscan investigation). In our own UK population the adoption of cMR T2\* scanning has been associated with a more than 70% reduction in cases of fatal heart failure, an experience that has been replicated in Cyprus, in Italy and other countries. Overall care has improved. A recent analysis of our patients with more than 10 years follow up revealed that only 23% now have any evidence of heart iron accumulation (T2\* less than 20 ms), compared to 60% of patients 10 years ago, with only 7% having severe iron overload (T2\* less than 10 ms), compared to 17% a decade ago.

## **Managing thalassaemia patients**

Optimal management of individuals needs close co-operation between clinicians of widely different specialties, probably best orchestrated by the prime provider of care, the haematologist. Regular assessments of the burden of iron overload are necessary for successful care, but cMR can be a scarce resource, even in our NHS. Thus good clinical judgement is required to marshal available funds, allied to a program of regular cardiovascular assessment using all the currently available diagnostic tools of cardiovascular medicine, especially high quality echocardiography (ultra-sound scanning). The echo can give early warning that the heart function is beginning to change and alert the individual and his clinicians that careful reassessment of treatment is needed. The much "loved" ejection fraction (EF) is often used as a measure of heart function. However a single parameter is not enough to fully describe the integrated function of the heart and the circulatory system, you would not wish to define a car's ability by quoting it's horsepower alone. Carefully undertaken echo, preferably following a specific protocol for the special issues affecting the thalassaemia population, is required and within the gift of any well run cardiology department. Interpretation of the results may take more knowledge and experience in this particular field, but in the modern era of electronic communication this should be relatively straightforward to engineer.

## **Cardiac arrhythmia and heart block**

Although there have been remarkable advances in the management and survival in thalassaemia, clinical problems remain common and new issues are beginning to become more prevalent, including atrial fibrillation (AF) in non-iron overloaded patients. Atrial fibrillation is a common rhythm disturbance in medicine, seen in many adults with diverse forms of heart problems, from high blood pressure to coronary artery disease. The rhythm may be intermittent (paroxysmal AF) or more persistent. In some patients AF is permanent. During AF the low pressure cardiac chambers (the atria) cease to beat regularly (fibrillate) and the overall beating of the heart often is rapid at the outset and is irregular in timing and irregular in the power of the pulse. For the patient this may be sensed as a fast, often irregular, heart beat. The efficiency of the heart is diminished, by about 15 to 20 %, which can be tolerated by those with good pump function, but can precipitate heart failure if the heart muscle in the ventricles is weakened. In the past, AF was commonly the harbinger of severe heart failure in heavily iron overloaded patients and thus gained a very ominous prognosis. Now the commonest presentation is decades after the resolution of cardiac iron overload, in thalassaemic patients with a very good outlook. Thus AF has moved from being a clinically severe and dreaded complication of iron overload,

to a more benign outlook, requiring management, but not being associated with dire outcomes in those with no iron and good heart function.

A major complication of AF in other medical conditions is stroke. The risk varies according to the underlying clinical condition, but may lie between 1 to 10 % per year. Thalassaemia patients often have an associated abnormality of coagulation and potentially would be at higher than average risk. The risk is minimal for AF that is of short duration (less than 24 hrs) and intermittent, but requires formal anti-coagulation as a precaution against stroke if permanent, or frequent and more than transient (greater than 24 hr episodes). Drugs to prevent attacks of AF have been disappointing in their success rates. There are few drugs than can be used to successfully prevent AF attacks and each must be used with care to prevent side effects; a cardiologist familiar with their use must monitor these medications. In recent years non-invasive techniques have been developed to treat AF and prevent recurrences. These non-surgical electro-physiological techniques are performed by specialised cardiologists (EP specialists) and consist of catheter-based methods to alter the electrical characteristics of the atria. Success rates of catheter ablation of AF are in the region of 70 to 80% with recurrences requiring repeat procedures in about 15% of cases. Our experience suggests that success rates are lower and the difficulty of the procedures is higher in the thalassaemic population, due to the multi-focal nature of AF in this patient group. It is likely that in the future, as experience increases, the success of ablation will improve and patients will be referred earlier, rather than waiting until the rhythm is firmly established. In addition it must be ensured that there are no structural abnormalities within the heart that would increase the risk of stroke, such as persistent small holes communicating the atrial chambers (called a PFO, or, if larger, an ASD), or valve disease. Finally, there is interest in methods to close off the source of clots producing strokes in AF. This is the (left) atrial appendage closure device, which can be placed with a simple non-general anaesthetic procedure, as a day case in those individuals at particular stroke risk. In the early years of recognition of thalassaemia as a distinct clinical condition, it was noted that many patients (up to 40%), who were transfused, but did not have access to regular effective chelation, developed problems with cardiac conduction. The most important of these complications was “complete heart block” (CHB). Although serious and a cause of fainting or collapse, CHB is straightforwardly treated by the implantation of a permanent pacemaker. This is a small electronic device implanted under local anaesthesia, which restores normal cardiac electrical conduction and the heart’s responsiveness to exercise and other increased demands. Unfortunately the metal components of pacemakers make them incompatible with MRI scanning, a potentially disastrous consequence for

thalassaemia patients, removing the most important tool for monitoring iron load. Thankfully, new technology has come to the aid of this group of patients. There are now readily available MR magnet compatible pacemakers and leads. For the now, thankfully rare patient requiring this treatment the implanting cardiologist must be made aware of the imperative to use such devices and no others.

## **Conclusion**

Thus although there is much to be confident about in patients with thalassaemia there still remain challenges to provide optimal quality of life. It remains to be emphasized that generally looking after one's health is important for all of us, but the thalassaemia population have potentially much more to gain (or lose), so that non-specific measures, such as quitting smoking, taking exercise, avoiding excessive weight gain are all vitally important to enjoy a healthier and longer life.

## **Further information is available via the websites below.**

[www.cardiosmart.org](http://www.cardiosmart.org) - this is somewhat American in outlook, but detailed and the information, particularly on devices is accurate & up to date. Easy to navigate & look up things.

[www.bhf.org.uk](http://www.bhf.org.uk) - lots of patient information leaflets and sign posts to useful sites and patient groups

[www.arrythmiaalliance.org.uk](http://www.arrythmiaalliance.org.uk) - lots of useful information on AF & other arrhythmia

[www.heartfailurematters.org](http://www.heartfailurematters.org) - detailed on heart failure, but mostly as applicable to a much older population with the common causes of heart failure, such as heart attack & blood pressure

[www.bcs.com](http://www.bcs.com) - lots of links to useful sites in UK & Europe