CFS - The Central Cause: Mitochondrial Failure

From DoctorMyhill

Published papers

- 16th January 2009 saw the publication of "Chronic Fatigue Syndrome and Mitochondrial Dysfunction", our paper (authors: Prof Norman Booth of Oxford University, Dr John McLaren-Howard of Acumen Laboratory and myself) presenting evidence that chronic fatigue syndrome has a physical basis. The paper was published in the International Journal of Clinical and Experimental Medicine. The full text of the paper can be accessed by clicking on this link **"Chronic Fatigue Syndrome and Mitochondrial Dysfunction"** (http://www.ijcem.com/files/IJCEM812001.pdf)

Since its original publication, our article has also now appeared on PubMed, which is the free digital archive of biomedical and life sciences journal literature hosted by the U.S. National Institutes of Health. The paper can be accessed via **this PubMed link (http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2680051)**.

- Our second paper, **Mitochondrial dysfunction and the pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) (http://www.ijcem.com/files/IJCEM1204005.pdf)** by the same three authors, was published in the International Journal of Clinical and Experimental Medicine on 30 June 2012. (PubMed link **Mitochondrial dysfunction and the pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) (http://www.ncbi.nlm.nih.gov/pubmed/22837795)**)

- November 2012 saw the publication of our third paper entitled "Targeting mitochondrial dysfunction in the treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) – a clinical audit". The full text of the paper is available from **the Journal's website (http://www.ijcem.com/files/IJCEM1207003.pdf)** (PubMed link **Targeting mitochondrial dysfunction in the treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) – a clinical audit (http://www.ncbi.nlm.nih.gov/pubmed/23236553)**)

Introduction

I think this is one of the most important handouts I have ever produced in terms of my understanding of CFS and what to do in order to recover! So please read this very carefully and several times over because for many sufferers it contains the keys to unlock their illness!

A very useful analogy is to think of the body as a car. What supplies the energy and the power to make that car work is the engine. Effectively mitochondria are the engines of our cells - they supply the energy necessary for all cellular processes to take place.

We are made up of lots of different cells - heart, blood, muscle nerve cells etc. All these cells are different because they all have a different job of work to do. To do this job of work requires energy. But the way in which energy is supplied is the same for every cell in the body. Indeed all animals share this same system. The mitochondria in my dog, my cat and my horse are exactly the same as mine. Mitochondria are a common biological unit across the animal kingdom. Energy is supplied to cells by mitochondria which I think of as little engines which power every cell in the body.

Chronic fatigue syndrome is the symptom caused by mitochondrial failure

The job of mitochondria is to supply energy in the form of ATP (adenosine triphosphate). This is the universal currency of energy. It can be used for all sorts of biochemical jobs from muscle contraction to hormone production. When mitochondria fail, this results in poor supply of ATP, so cells go slow because they do not have the energy supply to function at a normal speed. This means that all bodily functions go slow.

Every cell in the body can be affected

The following explains what happens inside each cell:

ATP (3 phosphates) is converted to ADP (2 phosphates) with the release of energy for work. ADP passes into the mitochondria where ATP is remade by oxidative phosphorylation (ie a phosphate group is stuck on). ATP recycles approximately every 10 seconds in a normal person - if this goes slow, then the cell goes slow and so the person goes slow and clinically has poor stamina ie CFS.

Problems arise when the system is stressed. If the CFS sufferer asks for energy faster than he can supply it, (and actually most CFS sufferers are doing this most of the time!) ATP is converted to ADP faster than it can be recycled. This means there is a build up of ADP. Some ADP is inevitably shunted into adenosine monophosphate (AMP -1 phosphate). But this creates a real problem, indeed a metabolic disaster, because AMP, largely speaking, cannot be recycled and is lost in urine.

Indeed this is the biological basis of poor stamina. One can only go at the rate at which mitochondria can produce ATP. If mitochondria go slow, stamina is poor.

If ATP levels drop as a result of leakage of AMP, the body then has to make brand new ATP. ATP can be made very quickly from a sugar D-ribose, but D-ribose is only slowly made from glucose (via the pentose phosphate shunt for those clever biochemists out there!). This takes anything from one to four days. So this is the biological basis for delayed fatigue.

However there is another problem. If the body is very short of ATP, it can make a very small amount of ATP directly from glucose by converting it into lactic acid. This is exactly what many CFS sufferers do and indeed we know that CFS sufferers readily switch into anaerobic metabolism. However this results in two serious problems - lactic acid quickly builds up especially in muscles to cause pain, heaviness, aching and soreness ("lactic acid burn"), secondly no glucose is available in order to make D-ribose! So new ATP cannot be easily made when you are really run down. Recovery takes days!

When mitochondria function well, as the person rests following exertion, lactic acid is quickly converted back to glucose (via-pyruvate) and the lactic burn disappears. But this is an energy requiring process! Glucose to lactic acid produces two molecules of ATP for the body to use, but the reverse process requires six molecules of ATP. If there is no ATP available, and this is of course what happens as mitochondria fail, then the lactic acid may persist for many minutes, or indeed hours causing great pain. (for the biochemists, this reverse process takes place in the liver and is called the Cori cycle).

Treatment package for failing mitochondria

The biological basis of treatment is therefore explained:

- **Pace** - do not use up energy faster than your mitos can supply it.

- **Feed the mitochondria** - supply the raw material necessary for the mitochondria to heal themselves and work efficiently. This means feeding the mitos correctly so they can heal and repair.
- Address the underlying causes as to why mitochondria have been damaged. This must also be put in place to prevent ongoing damage to mitos. In order of importance this involves:
- Pacing activities to avoid undue stress to mitos
- Getting excellent sleep so mitos can repair
- Excellent nutrition with respect to:
    - taking a good range of micronutrient supplements
    - stabilising blood sugar levels
    - identifying allergies to foods
- Detoxifying to unload heavy metals, pesticides, drugs, social poisons (alcohol,tobacco etc) and volatile organic compounds, all of which poison mitos.
- Addressing the common problem of hyperventilation
- Address the secondary damage caused by mitochondrial failure such as immune disturbances resulting in allergies and autoimmunity, poor digestive function, hormone gland failure, slow liver detoxification.

And now for a bit of good news! AMP can be recycled, but slowly. Interestingly, the enzyme which does this (cyclic AMP) is activated by caffeine! So the perfect pick-me-up for CFS sufferers could be a real black organic coffee with a teaspoon of D-ribose!

All the nutritional supplements that make up the basic nutritional package as well as provide specific support for mitochondrial function can be bought in my online shop - please visit shop sections Mitochondrial Package (http://www.salesatdrmyhill.co.uk/a-mitochondrial-package-starter-kit-1x-ubiquinol-1x-acetyl-lcarnitine-1x-d-ribose-1x-niacinamide-timed-release-315-p.asp) **Basic package (http://www.salesatdrmyhill.co.uk/the-basic-package---what-we-should-all-be-taking-to-live-to-our-full-potential-2-c.asp)** and **Improving energy - mitochondrial, adrenal and thyroid support (http://www.salesatdrmyhill.co.uk/improving-energy---mitochondrial-adrenal-and-thyroid-support-16-c.asp)**.

A Vital Test in Chronic Fatigue Syndrome

The central problem of chronic fatigue syndrome is mitochondrial failure resulting in poor production of ATP. ATP is the currency of energy in the body and if the production of this is impaired then all cellular processes will go slow. It is not good enough to measure absolute levels of ATP in cells since this will simply reflect how well rested the sufferer is. The perfect test is to measure the rate at which ATP is recycled in cells and this test has now been developed by John McLaren Howard. He calls it "ATP profiles". It is a test of mitochondrial function.

Not only does this test measure the rate at which ATP is made, it also looks at where the problem lies. Production of ATP is highly dependent on magnesium status and the first part of the test studies this aspect.

The second aspect of the test measures the efficiency with which ATP is made from ADP. If this is abnormal then this could be as a result of magnesium deficiency, of low levels of Co-enzyme Q10, low levels of vitamin B3 (nicotinamide adenine dinucleotide NAD) or of acetyl L-carnitine.

The third possibility is that the protein which transports ATP and ADP across mitochondrial membrane is impaired and this is also measured.

The joy of the ATP profiles test is that we now have an objective test of chronic fatigue syndrome which clearly shows this illness has a physical basis. This test clearly shows that cognitive behaviour therapy, graded exercise and anti-depressants are irrelevant in addressing the root cause of this illness.

To get the full picture I recommend combining this test with measuring levels of Co-enzyme Q10, SODase, Glutathione Peroxidase, L-carnitine, NAD and cell-free DNA. Cell free DNA is very useful because it reflects severity of the illness. When cells are damaged and die, they release their contents into the blood stream - cell free DNA measures the extent of this damage. The levels which come back are similar to those from patients recovering from major infections, trauma, surgery or chemotherapy - so this test puts CFS firmly in the realms of major organic pathology. SODase is an important antioxidant which mops up the free radicals produced in all the inefficient chemical reactions in the cells. Dr John McLaren-Howard has recently developed a serum L-carnitine test and made it available in September 2009. I have now included it in the **Mitochondrial Function Profile**.

For the ordering process and payment methods, please see **Ordering Tests**.

One other important co-factor in the production of energy in cells is D-ribose. It is used up so quickly by cells that measuring levels is unhelpful, but low levels of ATP imply low levels of D-ribose.

CFS is low cardiac output secondary to mitochondrial malfunction

Two papers have come to my notice recently which make great sense of both my clinical observations and also the idea that CFS is a symptom of mitochondrial failure. The two symptoms I am looking for in CFS to make the diagnosis is firstly very poor stamina and secondly delayed fatigue. I think I can now explain these in terms of what is going on inside cells and the effects on major organs of the body (primarily the heart). More importantly, there are major implications for a test for CFS and of course management and recovery.

If mitochondria (the little engines found inside every cell in the body) do not work properly, then the energy supply to every cell in the body will be impaired. This includes the heart. Many of the symptoms of CFS could be explained by heart failure because the heart muscle cannot work properly. Cardiologists and other doctors are used to dealing with heart failure due to poor blood supply to the heart itself. In CFS the heart failure is caused by poor muscle function and therefore strictly speaking is a cardiomyopathy. This means the function of the heart will be very abnormal, but traditional tests of heart failure, such as ECG, ECHOs, angiograms etc, will be normal.

Thanks to work by Dr Arnold Peckerman (**see here (http://www.name-us.org/ResearchPages/ResearchArticlesAbstracts/CirculatoryArticles/PeckermanImpedanceCardio.pdf)**) we now know that cardiac output in CFS patients is impaired. Furthermore the level of impairment correlates very closely to the level of disability in patients. Dr Peckerman was asked by the US National Institutes of Health to develop a test for CFS in order to help them to judge the level of disability in patients claiming Social Security benefits. Peckerman is a cardiologist and on the basis that CFS patients suffer low blood pressure, low blood volume and perfusion defects, he surmised CFS patients were in heart failure To test this he came up with Q scores.

"Q" stands for cardiac output in litres per minute and this can be measured using a totally non-invasive method called Impedence Cardiography. This allows one to accurately measure cardiac output by measuring the electrical impedence across the chest wall. The greater the blood flow the less the impedance. This can be adjusted according to chest and body size to produce a reliable measurement (this is done using a standard algorithm). It is important to do this test when supine and again in the upright position. This is because cardiac output in healthy people will vary from 7 litres per min when lying down to 5 litres per min when standing. In healthy people this drop is not enough to affect function. But in CFS sufferers the drop may be from 5 litres lying down to 3.5 litres standing up. At this level the sufferer has a cardiac output which causes borderline organ failure. There are further papers concerning Cardiovascular/Circulatory Research and CFS/ME at NAME-US.org (http://www.name-us.org/ResearchPages/ResCirculatory.htm)

This explains why CFS patients feel much better lying down. They have acceptable cardiac output lying down, but standing up they are in borderline heart and organ failure. CFS is therefore the symptom which prevents the patient developing complete heart failure. Actually, everyone feels more rested when they are sitting down with their feet up! The subconscious has worked out that the heart has to work less hard when you are sitting down with your feet up - so we do so because we feel more comfortable!

Low cardiac output explains the symptoms of CFS

The job of the heart is to maintain blood pressure. If the blood pressure falls, organs start to fail. If the heart is working inadequately as a pump then the only way blood pressure can be sustained is by shutting down blood supply to organs. Organs are shut down in terms of priority, i.e. the skin first, then muscles, followed by liver, gut, brain and finally the heart, lung and kidney. As these organ systems shut down, this creates further problems for the body in terms of toxic overload, susceptibility to viruses which damage mitochondria further, thus exacerbating all the problems of the CFS sufferer. This is called POTS Postural orthostatic tachycardia syndrome or POTs

Dr Paul Cheney has explored this further with his work with cardiac output in CFS - see Dr Cheney on heart function

Chest pain

This is a common symptom in CFS. Chest pain results when energy delivery to the muscles is impaired. There is a switch to anaerobic metabolism, lactic acid is produced and this results in the symptom of angina. Doctors recognise one cause ie poor blood supply, ie the supply of fuel and oxygen is impeded. However this fuel and oxygen has to be converted to ATP by mitochondria, so if this is slow, the same symptom of angina will result.

One molecule of sugar, when burnt aerobically by mitochondria, will produce 36 molecules of ATP. In anaerobic metabolism, only 2 molecules of ATP are produced. This is very inefficient and lactic acid builds up quickly. The problem is that to convert lactic acid back to sugar (pyruvate) 6 molecules of ATP are needed (the Cori cycle). So in CFS the chest pain is longer lasting because this conversion back is so slow. Clinically this does not look like typical angina. Many patients are told they have non-typical chest pain with the implication that nothing is wrong! Actually, they have mitochondrial failure in the heart.

Effects on the Skin

If you shut down the blood supply to the skin, this has two main effects. The first is that the skin is responsible for controlling the temperature of the body. This means that CFS patients become intolerant of heat. If the body gets too hot then it cannot lose heat through the skin (because it has no blood supply) and the core temperature increases. The only way the body can compensate for this is by switching off the thyroid gland (which is responsible for the level of metabolic activity in the body and hence heat generation) and so one gets a compensatory underactive thyroid. This alone worsens the problems of fatigue.

The second problem is that if the micro-circulation in the skin is shut down, then the body cannot sweat. This is a major way through which toxins, particularly heavy metals, pesticides and volatile organic compounds are excreted. Therefore the CFS sufferer's body is much better at accumulating toxins, which of course further damage mitochondria.

Symptoms in Muscles

If the blood supply to muscles is impaired, then muscles quickly run out of oxygen when one starts to exercise. With no oxygen in the muscles the cells switch over to anaerobic metabolism, which produces lactic acid and it is this that makes muscles ache so much.

As well as the above problem, muscles in the CFS patient have very poor stamina because the mitochondria which supply them with energy are malfunctioning.

Symptoms in the Liver and Gut

Poor blood supply to the gut results in inefficient digestion, poor production of digestive juices and leaky gut syndrome. Leaky gut syndrome causes many other problems such as allergies, autoimmunity, malabsorption, etc., which further compound the problems of CFS.

If liver circulation is inadequate, this will result in poor detoxification, not just of heavy metals, pesticides and volatile organic compounds, but also toxins produced as a result of fermentation in the gut again further poisoning the mitochondria.

Effects on the Brain

In October 2007 I attended a conference sponsored by the late Dr John Richardson. A Canadian physician Dr Byron Hyde showed us some functional scans of the brains of CFS patients. If I had not known the diagnosis, I would have diagnosed strokes. This is because the blood supply to some area of the brain was so impaired. The default is temporary and with rest, blood supply recovers. However, this explains the multiplicity of brain symptoms suffered from, such as poor short term memory, difficulty multi-tasking, slow mental processing and so on. Furthermore, brain cells are not particularly well stocked with mitochondria and therefore they run out of energy very quickly.

Effects on the Heart

There are two effects on the heart. The first effect of poor micro-circulation to the heart is disturbance of the electrical conductivity which causes dysrhythmias. Many patients with chronic fatigue syndrome complain of palpitations, missed heart beats or whatever. This is particularly the case in patients with poisoning by chemicals since the chemicals are also directly toxic to nerve cells.

The second obvious result is poor exercise tolerance. Heart muscle fatigues in just the same way that other muscles fatigue. Symptomatically this causes chest pain and fatigue. In the longer term it can cause heart valve defects because the muscles which normally hold the mitral valve open also fatigue.

The difference between this type of heart failure and medically recognised congestive cardiac failure is that patients with CFS protect themselves from organ failure because of their fatigue symptoms. Patients with congestive cardiac failure initially do not get fatigue and often present with organ failures such as kidney failure or overt heart failure. At present I do not know why there is this difference.

> *This approach to treating Heart Disease is exactly the same regardlees of the conventionaol diagnosis*.

So patients with angina, high blood pressure, heart failure, cardiomyopathy, some valve defects as well as patients with cardiac dysrhythmias also have mitochondrial problems and will respond in the same way to nutritional therapies and detox therapies.

Effects on Lung and Kidney

The lung and kidney are relatively protected against poor micro-circulation because they have the largest renin angiotensin system, which keeps the blood pressure up in these vital organs. Therefore clinically one does not see patients with kidney failure or pulmonary hypoperfusion in CFS.

Explanation of the Fatigue Problems in CFS Patients

Energy to the body is supplied by mitochondria, which firstly produce NAD (nicotinamide adenosine diphosphate) from Kreb's citric acid cycle and this is used to power oxidative phosphorylation which generates ATP (adenosine triphosphate). These molecules are the "currency" of energy in the body. Almost all energy requiring processes in the body have to be "paid for" with NAD and ATP, but largely ATP. The reserves of ATP in cells are very small. At any one moment in heart muscle cells there is only enough ATP to last about ten contractions. Thus the mitochondria have to be extremely good at re-cycling ATP to keep the cell constantly supplied with energy.

If the cell is not very efficient at re-cycling ATP, then the cell runs out of energy very quickly and this causes the symptoms of weakness and poor stamina. The cell literally has to "hibernate" and wait until more ATP has been manufactured.

In producing energy, ATP (three phosphates) is converted into ADP (two phosphates) and ADP is re-cycled back through mitochondria to produce ATP. However, if the cell is pushed (ie stressed) when there is no ATP about, then it will start to use ADP instead. The body can create energy from ADP to AMP (one phosphate), but the trouble is that AMP cannot be re-cycled. The only way that ADP can be regenerated is by making from fresh ingredients, but this takes days to do. This explains the delayed fatigue seen in chronic fatigue syndrome.

So to summarise, the basic pathology in CFS is slow re-cycling of ATP to ADP and back to ATP again. If patients push themselves and make more energy demands, then ADP is converted to AMP which cannot be recycled and it is this which is responsible for the delayed fatigue. This is because it takes the body several days to make fresh ATP from new ingredients. When patients overdo things and "hit a brick wall" this is because they have no ATP or ADP to function at all.

Implications for Treatment

Many patients I see get well with my standard work up with respect to vitamins and minerals, diet, pacing and sleep. However many need the **specific package of supplements**, to further support mitochondria which includes D-ribose, CoQ10, acetyl-l-carnitine, NAD, magnesium and B12 injections. All these things must be put in place to repair and prevent ongoing damage to mitochondria so allowing them to recover. For mitochondria to recover they need all the essential vitamins, minerals, essential fatty acids and amino acids to manufacture the cellular machinery to restore normal function. The mitochondrial function tests then allow us to identify lesions which can be corrected by attention to nutritional supplements, improving antioxidant status, detoxing, hyperventilation or whatever. CFS sufferers have limited reserves of physical, mental and emotional energy and this test allows us to direct those energies into the most fruitful line of approach.

Clinically the above issues mean that there are two clear stages of fatigue:

1. Mild chronic fatigue syndrome - in mild fatigue there is mild failure of mitochondria. If mitochondria go slow then cells go slow. If cells go slow then organs go slow. The body will become generally less efficient. So for example somebody mildly affected would not be able to increase their fitness - if they try to exercise they would quickly switch into lactic acid metabolism and would be forced to stop. Indeed we now know that mitochondria are responsible for controlling the normal ageing process. Therefore many of the symptoms and diseases associated with ageing are actually the result of mitochondrial function declining. Indeed many of these ageing diseases have now been attributed to mitochondrial failure such as loss of tissues (loss of muscle bulk), organ failures, neurodegenerative conditions, heart disease and cancer. Many symptoms which are attributed to ageing are due to mitochondria. It is not that we can stop the mitochondria from ageing, but we can certainly slow it all down using good nutrition, good diet, freedom from toxic stress, healthy lifestyles and so on.
2. Severe chronic fatigue syndrome - in severe chronic fatigue all the above factors apply. However, there is an additional problem. The most metabolically demanding organ in the body is the heart and if mitochondria cannot supply the heart with sufficient energy then the heart

will go into a low output state. This compounds the problem of all mitochondria. If the heart is in a low output state then blood supply is poor and therefore the fuel and oxygen necessary for the engine to work are also impaired. So this compounds all the above problems and makes them proceed even more quickly and people end up with greater disability.

I suspect it is a combination of the underlying poor mitochondrial function, which then suddenly becomes critical when it comes to cardiac output, which precipitates a much more severe illness in someone who is already compromised.

Related Tests

- **Mitochondrial Function Profile**

Related Articles

- **"Oxidative Stress and Mitochondrial Injury in Chronic Multisymptom Conditions: From Gulf War Illness to Autism Spectrum Disorder"** - an interesting new paper published in Nature Precedings 2012.

- **ME International Consensus Primer for Medical Practitioners** has just been published online (October 2012) by the Myalgic Encephalomyelitis (ME) International Consensus Panel. This is the clinical practice companion to another important publication by the International Consensus Panel. In October 2011 the Panel published in the Journal of Internal Medicine **Myalgic encephalomyelitis: International Consensus Criteria**.

External links

- **Sales at Dr Myhill (http://www.salesatdrmyhill.co.uk)** stocks all the nutritional supplements I recommend.
- A recent paper (May 2015) entitled **'"In silico analysis of exercise intolerance in myalgic encephalomyelitis/chronic fatigue syndrome"'**, published by Nicor Lengert and Barbara Drossel in the journal **"Biophysical Chemistry"**, provides further confirmation of my jointly published papers. Under an assumed reduced mitochondrial capacity for CFS patients, simulations exhibit critically low levels of ATP and very importantly describe exquisitely the cardinal symptom of prolonged recovery time after minimal activity. In essence, and under the assumption of reduced mitochondrial capacity in CFS patients, which has been demonstrated to be the case in my medical papers linked above, this new paper models the biophysical processes that would follow from such an assumption. The conclusions are that 1-- Recovery time after minimal activity will be very prolonged, 2--Critically low levels of ATP will result 3 - Increased acidosis results and 4 - Lactate accumulation also results. The paper can be viewed by clicking on the four links below, as described:
    - **Full Text of paper "In silico analysis of exercise intolerance in myalgic encephalomyelitis/chronic fatigue syndrome"**
    - **Supplementary Information including sensitivity analysis**
    - **Description of Model Constants used in the simulation**
    - **Graphical representation of CFS Factor against ATP usage and the effect on lactate, recovery time and increases in AMP**

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