31 March 2008

Hannah Poling Autism-Vaccine Case:
Implications for ME/CFS-labelled patients
By Lara

Abstract

When Hannah Poling was 19 months old she was administered 9 vaccines simultaneously and just 48 hours afterwards, her health began to deteriorate. She developed a fever and her temperature soared to 38.9°C. She cried inconsolably, was irritable, lethargic and refused to walk. Over the next 4 months her growth and movement decreased, rashes appeared on her abdomen and she began to display autistic behaviours including fixation on television, poor eye contact, spinning and disrupted sleep. Tests and muscle biopsy carried out by her father (a neurologist at John Hopkins University in the USA) and his colleagues indicated specific genetic mutations in her mitochondrial DNA (mt-DNA), Type 1 muscle fibre atrophy and abnormal levels of various metabolic products in her blood stream (elevated lactic acid, serum creatine kinase level, and aspartate aminotransferase). The findings were published in the Journal of Clinical Pathology along with a retrospective study of 159 other ASD patients. [1] Hannah's parents applied for vaccine damages in order to pay for the 'one-to-one' specialist care that she will probably require for the rest of her life. In 2007, the U.S. Department of Health and Human Services (DHHS) made the decision to award the Poling family compensation from the federal vaccine injury fund after they conceded that immunisations given to her at 19 months old had aggravated a rare underlying mitochondrial condition that resulted in a brain disorder 'with features of autism spectrum disorder'.

The outcome of this case has raised questions about how safe vaccines are for those with potentially undiagnosed metabolic or mitochondrial disorders. It has been claimed by government-appointed experts that such disorders are rare, but a review of available literature does not tally with this conclusion. In this paper the basic scientific background on metabolic and mitochondrial disorders, their prevalence, origin and precipitating factors are described. Overall, it appears that metabolic disorders are far from rare and may in fact be widespread.

Faulty metabolic and mitochondrial processes are also well documented in patients labelled with ME/CFS and this may be due to an inherited mitochondrial disorder and/or exposure to environmental pollutants and/or pathogens with a particular toxicity for mitochondrial DNA (mt-DNA). This hypothesis may better account for symptoms than that of the 'aberrant immune response' to environments that normal controls are able to withstand. Although some researchers claim that studies of immune markers validate such a conclusion, it is hard to see how this could be reliable without a proper study of the structure of mt-DNA and associated cellular energy production. Certainly the hypothesis that 'stressors' (including psychological stress) cause an aberrant immune response is not born out by patients' experience with psychosocial treatments (e.g. tricyclic anti-depressants, CBT/GET). Patients have not reported positive results with such treatments in fact the opposite, with many claiming it made their symptoms worse. This is not surprising if there is insufficient cellular energy available in the mitochondria to cope with the demands of exercise programmes and furthermore it is known that drugs such as Amitriptyline and Prozac can make mitochondrial functioning worse. Combining exercise with such drugs therefore seems to be the worst possible treatment to offer those with underlying mitochondrial dysfunctions and poor energy production.

Various tests for metabolic and mitochondrial status are now available, some via the NHS but they are not all included in the NICE CFS/ME Guidelines. Some are available privately and have been shown to be predictive of the level of patient disability. It is hoped that this paper will assist the ME/CFS patient community in making informed decisions about having immunizations, treatments for their illness as well as providing information about where to

get tested privately for metabolic disorders, in some cases at relatively small cost. The possibility for immunisations as a causal factor in ME/CFS has also considered in light of patient reports and medical evidence published to date.

Introduction

In the aftermath of the Hannah Poling case and considering the awful reality of the symptoms of Autism/ASD, one might have expected an intelligent and adult debate on how this situation could be prevented from recurring. Instead, so-called ‘experts’ and government have been furiously back-pedalling and giving out mixed messages and blatant disinformation regarding the nature and prevalence of metabolic diseases. The US Centers for Disease Control (CDC) claimed that even though the Federal Court accepted that in Hannah’s case the vaccines aggravated an apparently inherited mitochondrial disorder, this has no wider implications and in no way provides proof that vaccines can cause ASD. Meanwhile in the UK media, the issue was barely mentioned.

However, since the case was publicised, the unease surrounding mitochondrial disorders vaccines and Autism/ASD seems to have been growing rather than dying down. In the last couple of weeks alone, the CDC has held more than one conference call to debate the issue with various experts. The content of the calls has not lead to a reassuring conclusion that the risks of vaccination in children with potential genetic mitochondrial disease are fully understood or preventable. [2] One researcher, Dr Ed Trevathan commented that:

‘The truth is we don't know the exact prevalence of mitochondrial disorders in the general population. Those data are somewhat difficult to determine. One of the reasons, by the way is because mitochondrial disorders are extremely difficult technically to diagnose, at least in terms of verifying the mitochondrial DNA abnormality. Diagnosis often requires either multiple blood draws or more often muscle biopsies. There have even been cases in which brain biopsies have been required to make the diagnosis.’

Later in the call, another researcher Dr Thomas Insel stated that:

‘when you have a genetic lesion in your mitochondrial DNA you're likely to develop a whole range of problems due to environmental stressors.’

Oddly, Trevathan then concludes that there is no need to test large numbers of children for mitochondrial disorders and that children with mitochondrial disorders may be vaccinated anyway depending on the individual physician’s ‘judgement’ of the risks.

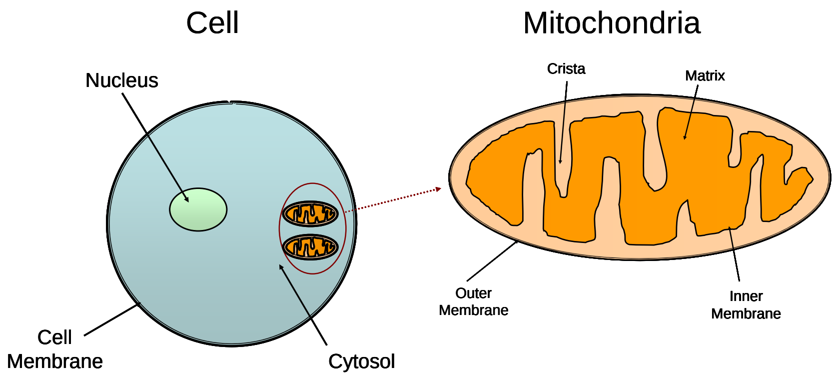
The outcome of the Hannah Poling case has clearly raised questions about the risks of vaccinations given to babies and individuals of all ages who may have potentially undiagnosed metabolic/mitochondrial disorders. In order to answer these appropriately a look at the science of cellular energy and how it can be disrupted before or during the course of a disease is needed and its implications for ME/CFS-labelled patients given proper consideration.

Production of Cellular Energy

Cellular energy is produced in an extremely intricate process known as ‘Cell Respiration’. It involves a long chain of individual processes which must all work in tandem. The appropriate chemicals must be ‘in the right place at the right time’ in order for Cell Respiration to run efficiently – a little like a production line in a factory. This process occurs inside the cells in the human body and more specifically inside the ‘mitochondria’, which are the cells’ power houses (see Fig. 1). Input is also required from the cell nucleus and during energy production chemicals and signals feed back and forth between the mitochondria, moving through the cytosol (the internal fluid of the cell) and into the cell nucleus and vice versa. Any disruption to the Cell Respiration process can cause energy production to slow down. When this happens the person experiences ill health, poor organ functioning and an ‘exercise intolerance’ (a key feature of metabolic/mitochondrial disease).

The mitochondrion (plural mitochondria) shown in the picture below, has several functions including cell growth, death, signalling and differentiation but in particular, it is key to the Cell Respiration process and therefore energy production. Some cells in the body (mainly muscle and vital organs) contain very dense numbers of mitochondria as large amounts of energy are needed for them to function properly. Mitochondria have their own independent genome made up mostly of DNA (mt-DNA) which is maternally inherited, but they also rely on production of components in the nuclear DNA (n-DNA) so disorders can also be inherited from the father.

Fig 1. Schematic of a Human Cell and Mitochondrion

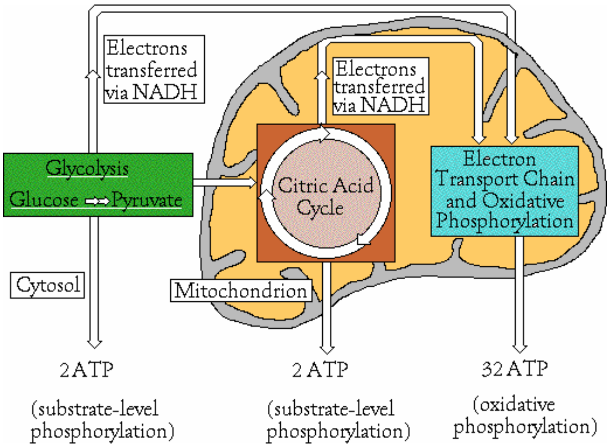


Energy production splits down into four stages, with the first taking place in the cell’s ‘Cytosol’ (outside of the mitochondria) and the following three inside the mitochondria (see Fig. 2). The ultimate goal is to produce a chemical known as Adenosine Triphosphate (ATP). The four stages leading to ATP production are:

1. Glycolysis. This process occurs in the cytosol. Glucose, a type of sugar obtained from dietary carbohydrate is split into 2 molecules of pyruvate and 2 ATP (net) are produced. If insufficient glucose is available, pyruvate can be made from glycerol which can be obtained in turn from the breakdown of fat (lipids) from food intake. Lactate is also produced via fermentation; this is unfavourable if it occurs excessively and in a normal healthy person, it only occurs briefly before pyruvate is transferred to the next stage in Cell Respiration – The Link Reaction.
2. The Link Reaction. This reaction takes place as pyruvate moves into the ‘mitochondrial matrix’ and is oxidised. Fatty acids from the breakdown of lipids can also be used to in the link reaction.
3. The Krebs Cycle. This is a series of reactions designed to provide negatively charged species called ‘electrons’ for the final stage of Cell Respiration (The Electron Transport Chain). It ‘turns’ twice, and produces 1 ATP for each turn, (2 in total).
4. The Electron Transport Chain. The final stage of respiration takes place in the inner mitochondrial membrane and produces the largest number of ATP molecules (32 in total) via a process called ‘Oxidative Phosphorylation’ (OXPHOS) and is therefore vital to energy production. The most serious metabolic diseases involve faulty OXPHOS operation in the mitochondria.

ATP molecules are effectively the body’s ‘charged batteries’. Once made, a chemical reaction called ‘hydrolysis’ converts ATP to energy and a by-product known as Adenosine Diphosphate (ADP). ADP molecules are effectively the body’s ‘uncharged batteries’ and they must be ‘recharged’ inside the body’s mitochondria back into ATP. The latter process (recycle of ADP back to ATP) takes place in stage 4 as above via the OXPHOS reaction in the Electron Transport Chain.

Fig.2 Simplified Schematic of Cell Respiration



The OXPHOS process is vital to energy production and if it breaks down, the majority of ATP will not be made properly. An OXPHOS dysfunction is therefore a disaster in metabolic terms and will cause a ‘supply-demand’ imbalance in energy requirements. If ATP is used up faster than it can be created various unfavourable processes take over. For instance, the body may use ADP instead and this is converted to a chemical known as Adenosine Monophosphate (AMP) in order to release more energy. However, AMP cannot easily be recycled back to ATP and is mostly broken down and lost in urine. This puts an additional load on the body to make fresh ATP from starting materials (sugars, vitamins, enzymes etc) which is a much slower process than ADP-ATP recycle.

The energy obtained from the ATP/ADP cycle enables a person to stand, walk, eat, lift and carry or to perform any energy-consuming actions. Even sitting at rest requires energy from ATP for normal functioning of vital organs, digestion, brain function etc. For aerobic exercise, the use and recycle of ATP has to speed up dramatically to pump out enough energy to keep up. E.g. for an athlete to run a marathon, or for someone to do a lengthy work out at the gym. Efficient Cell Respiration is therefore essential to life, functioning of body organs (e.g. the brain, heart, stomach, liver etc) and to having a normal exercise-tolerance’. This explanation of cell respiration and mitochondrial function is highly simplified and does not cover the highly intricate range of problems that can occur but will hopefully serve to contextualise the information and analysis of the Hannah Poling case and its implications for ME/CFS sufferers.

Energy Metabolism Disorders

Energy Metabolism disorders occur when:

- ATP is not sufficiently produced during Cell Respiration
- ATP cannot be ‘delivered’ efficiently into the cells that need them
- ATP cannot be recycled efficiently back from ADP
- Too much ATP is required in relation to supply. Some infections (‘energy parasites’) can cause rapid depletion of cellular ATP.

Sometimes these problems occur because of a genetic deficiency that is either inherited from one or both parents, or one which occurs over time due to external factors, the environment or because of aging. Inherited disorders include mitochondrial disease and metabolic myopathies. In the latter, the faulty biochemical processes take place outside of the mitochondria and these include glycogen storage diseases, lipid storage diseases and purine nucleotide disorders. Metabolic myopathies can cause major disruption to energy production and similar symptoms to mitochondrial diseases. For further information on metabolic disorders, the reader is referred to Katirji's excellent review in E-medicine in 2007. [3]

Mitochondrial Diseases, where the inherited gene causes faulty processes inside the mitochondria are grouped into sub-types and each has a different impact on mitochondrial performance and subsequently the resulting symptoms in the patient. The main types of mitochondrial diseases result from genomic faults that disrupt the expression of enzymes necessary for production of Adenosine Triphosphate (ATP) via Oxidative Phosphorylation (OXPHOS) in the Electron Transport Chain (ETC).

Table 1. Examples of Genetic Deficiencies in Mitochondrial Disease

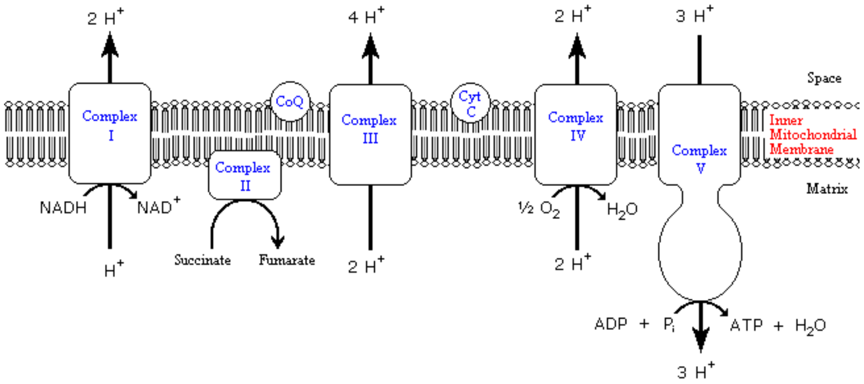
Category	**Other names**	**Examples of Symptoms**	**Examples of related diseases**	**OMIM Records**
Complex 1 Dysfunction	NADH:Q(1) OXIDOREDUCTASE DEFICIENCY	Exercise intolerance, muscle wasting, lactic acidosis, cardiomyopathy, poor growth	Leigh Disease, MELAS, MERRF, Pearson Syndrome,	#252010
Complex II Dysfunction	SUCCINATE CoQ REDUCTASE DEFICIENCY	Short-stature, cardiomyopathy, muscle weakness, loss of motor skills, ataxia,	Kearns-Sayre Syndrome, Leigh Disease	252011
Complex III Dysfunction	UBIQUINOL CYTOCHROME C REDUCTASE	tubulopathy, encephalopathy, liver failure, muscle weakness, myoclonus, ataxia, mental confusion, exercise intolerance, metabolic acidosis	Leigh Disease, Pearson Syndrome	124000
Complex IV Dysfunction	CYTOCHROME c OXIDASE DEFICIENCY	Diminished reflexes, lactic acidosis, proteinuria, glucosuria, and amino aciduria, liver failure,	Leigh Disease, MNGIE syndrome, Pearson Syndrome	220110
Complex V Dysfunction	ATP synthase	lactic academia, hypotonia, and neurodegenerative disease, retinitis pigmentosa, ataxia, and mental retardation, cardiomyopathy, lactic acidosis	Leigh Disease, NARP syndrome,	516060

Source: OMIM - 'The Online Mendelian Inheritance in Man' Database.
http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim

While mitochondria have their own genome and therefore produce their own DNA they are not completely autonomous and require some components (e.g. enzymes) to be made in the cell nucleus and transported through the cell into the mitochondria. So if the nuclear DNA (n-DNA) responsible for providing components to the mitochondria is faulty or has been disrupted in some way, mitochondrial diseases can develop. n-DNA is inherited 'autosomally' (i.e. from both parents) and this explains why some mitochondrial diseases do not come from the mother. To date at least 20 n-DNA mutations that been documented to cause mitochondrial disease and many more may remain unknown. [4]

Another point to note is that while mitochondrial DNA (mt-DNA) deletions and mutations may result in a specific disease, they may also be found in other diseases, although they may not necessarily have been proved to be contributing. Many mutations in mt-DNA are being found in cases of other neurodegenerative diseases. The mutations are not by and large yet believed to be 'causative' but to increase the statistical risk of such diseases taking into account other lifestyle and environmental factors. This will be discussed further below.

Fig. 3 Activity of Complex 1-V enzymes in the Electron Transport Chain.



The Poling Study

In Hannah Poling's case a particular genetic mutation in the mitochondrial genome in the '16S ribosomal RNA gene', which sits at the 'Ten O'clock' position in Fig.4, was found to be responsible for her faulty mitochondrial functioning. This genetic defect was aggravated by the simultaneous administration of 9 different vaccines when Hannah was 19 months old that caused inflammation in her brain (encephalitis) and she subsequently developed autistic symptoms including regression in her ability to speak, interact with others, bowel and gastrointestinal problems and poor growth.

Hannah's father Dr Jon Poling is a neurologist at John Hopkins Hospital in Baltimore, MD USA. In 2006, he and his colleagues published a study about his daughter's case as well as a retrospective analysis of 159 ASD patients. [1] Hannah underwent various blood tests as well as a muscle biopsy which showed that she was suffering with:

'Subtle abnormalities in the serum creatine kinase level, aspartate aminotransferase, and serum bicarbonate…type I myofiber atrophy, increased lipid content, and reduced cytochrome c oxidase activity. There were marked reductions in enzymatic activities for complex I and III. Complex IV (cytochrome c oxidase) activity was near the 5% confidence level.'

Poling et al were also able to identify several metabolic markers in blood tests and muscle biopsies for the other 159 ASD patients. These markers showed that 38% of the ASD patients had abnormal aspartate aminotransferase and 47% had raised creatine kinase. Poling et al emphasised the need for more reliable laboratory markers to detect abnormalities of mitochondrial function. Hannah was treated with nutritional supplements including CoEnzymeQ10, mitochondrial enzymes, L-carnitine and thiamine and has thankfully made considerable improvements, although she still requires 'one-on-one' help on a daily basis.

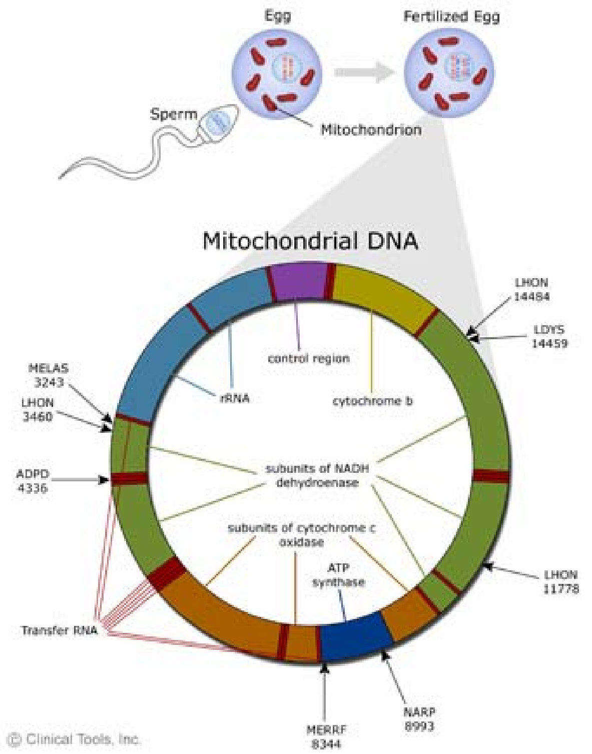
Subsequent to publication of the Poling case it was claimed that the specific genetic mutation found in Hannah's mt-DNA was rare and that cases of 'Mitochondrial Disease' are not very common. According to Lindsey Kent of the University of St Andrews in the UK, mitochondrial diseases affect only 5.7 per 100,000 individuals worldwide. [5] Mayr et al report that disorders of OXPHOS occur in 1 in 7,600 people (13.2 in every 100,000) over twice the level reported by Kent. [6] The Cleveland Clinic in the USA puts the figure at 1 in 4000 (25 per 100,000). [7] Several other studies also confirmed the presence of mitochondrial disorders in Autism/ASD sufferers that suggest within this patient group, the prevalence of mitochondrial disorders may be as high as 7-20%. This has lead researchers to suggest genetic testing and tailoring of therapeutic approaches in Autism/ASD patients. [8-16].

While a mt-DNA mutation may result in a specific disease, it may also be found in other diseases, although it may not necessarily be seen as causative. Many mutations in mt-DNA are being found in cases of other diseases such as Alzheimer's, Parkinson's and Huntington's Disease. [17] The mutations are not by and large yet believed to be 'causative' but to increase the statistical risk of such diseases taking into account other lifestyle and environmental factors. Chinnery et al reported that:

"although the classical mitochondrial encephalomyopathies are rare, mtDNA defects are relatively common, and probably contribute to the pathogenesis of many different diseases, many non-neurological, and they may also be involved in the ageing process itself." [18]

Alongside inherited genetic disorders, environmental factors are thought to be highly important in determining who will develop a particular disease. A gene on its own may not be enough to cause disease but mixed with a poor diet and lifestyle, the natural process of ageing, infection or one or more environmental toxins, or a combination of all of these, a gene may be altered or degraded in a manner which then brings on symptoms and disease.

Fig. 4 Schematic of the Mitochondrial Genome



Source: This information was provided by Clinical Tools, Inc., and is copyrighted by Clinical Tools, Inc.

Zhang et al discuss the mutations in mitochondrial DNA (mt-DNA) that occur during replication and conclude that this occurs as a result of interplay between 'ancient mitochondrial genes and the environment'. [19] Seeing as our ancestors did not suffer such high rates of neurological disease, its seems reasonable to suspect that it is the environment, including the pharmaceuticals prescribed to us, that has changed and that this is somehow incompatible with our genes. If genes and their prevalence in the population has been fairly constant for the last several centuries and longer (and presuming that they are not for any reason, mutating faster than normal) then why do we attribute increasing disease to their natural variations rather than to the rapid pace of environmental change that has been abundantly obvious around us?

Coppede et al, list metals, pesticides, foods, head injuries and infections as risk factors for neurodegenerative diseases and postulate an interplay between environment and metabolic enzymes as being involved in the onset of neurological diseases such as ALS, Alzheimer's and Parkinson's Disease. [20] Normally onset of such diseases is seen in the elderly after many years of potential exposure to environmental toxins combined with the natural aspects of aging. It is of particular concern therefore for serious neurodegenerative diseases such as Autism/ASD to be increasingly seen in infants before their third birthday.

We have to ask what possible environmental influences could cause the onset of neurodegenerative disease or symptoms linked to mitochondrial dysfunction in those who have not had a lifetime of environmental exposure? The notorious links between autism/ASD and mercury, especially thimerosal vaccine preservatives which were first introduced into vaccines in 1931, continue to be put forward by researchers. [21] Others dismiss such theories on the basis that thimerosal is being removed or limited in the formulation of some, but not all childhood vaccines. Flaws in this argument include the fact that thimerosal is still used in some vaccines administered to both infants and pregnant women and aluminium is also implicated in the onset of various neurodegenerative diseases and is still used in many vaccine adjuvants. The presence of live or 'attenuated' pathogens and their ability to 'return to virulence' is also a potential issue as outlined in the pharmaceutical industry's own patent filings. [22] Poling et al and others note that an infection could equally put an additional oxidative stress onto the operation of mitochondria with 'faulty' or 'abnormal' gene variants.

It appears that the potential for vaccination to exacerbate mitochondrial disease or dysfunction is unknown. Considering this lack of understanding as well as the fact that babies are not pre-screened for genetic mt-DNA mutations or ATP/OXPHOS function prior to vaccination, it is not clear how decisions on the effects of vaccinations could be taken without more research, in-depth testing and risk analysis. Certainly, as Poling and Chinnery have noted, routine blood testing of creatine kinase, liver enzymes and basic testing is not sufficient to diagnose mitochondrial dysfunction in a clinical setting. [1, 18]

There are many other papers covering the area of mitochondrial dysfunction and genetics than those listed here and it seems that this area of study is growing at a fast pace. On the this basis and with the arguments presented above, it is of no comfort to be told by doctors, government officials and health agencies that these disorders are extremely rare and should not affect our decision to have vaccinations or to allow our children to be vaccinated. Published and readily available scientific information does not appear to categorically support the reassurances being made by government and healthcare providers.

Mitochondrial Dysfunction & Sudden Infant Death Syndrome (SIDS)

Entries were found in the Online Mendelian Inheritance in Man (OMIM) database for SIDS. Surprisingly there have been multiple findings of mitochondrial and other biomedical abnormalities in SIDS victims with reports going back as far as 1976. [23] The summary of the relevant record (#272120) states that:

'A number sign (#) is used with this entry because mutations in the mitochondrial genes MTTL1 (590050) and MTND1 (516000) may play a role in some cases of SIDS. Evidence has also been presented for a relationship between SIDS and mutations in the SCN5A (600163), KCNQ1 (607542), and CAV3 (601253) genes, which cause various forms of long QT syndrome (see LQT1, 192500). There is also evidence for associations between SIDS and mutation in the SLC6A4 gene (182138) and the GPD1L gene (611778).'

The record refers to a paper published in 1998, which detailed a retrospective study of Fatty-Acid Oxidation (FAO) disorders in the post-mortem livers of 418 cases of SIDS. [24] The mt-DNA mutations found in some cases of SIDS have been associated with a breakdown in the Oxidative Phosphorylation (OXPHOS) process, required for energy production in the body similar to those found in ASD including the Poling study.

While similarities in mt-DNA mutations in ASD and SIDS cannot be taken as evidence of a pre-disposition to vaccine damage in all, it is an unhappy coincidence that the late Sally Clark lost two babies from SIDS; the first Christopher was uncharacteristically dozy after his vaccines and the second Harry, died just 5 hours after he was administered multiple vaccinations with DTP, Hib (Meningitis) and Polio. Sally went on to be tried for their murder, was jailed for three and a half years on the basis of the flawed testimony of discredited doctor Prof Roy Meadows. It does not appear that any genetic testing was carried out on either Christopher or Harry at autopsy, or that any of the existing evidence of mitochondrial and other genetic mutations was taken into account during Sally Clark’s trial nor the other women wrongfully imprisoned for their children’s deaths.

Implications for ME/CFS-labelled patients

Vaccines

The outcome of the Hannah Poling case may have extensive implications for ME/CFS-labelled patients. As with Autism/ASD patients there is also evidence for involvement of vaccines. Immunisations for the enterovirus (EV) poliomyelitis have a particularly poor safety history in general and have been implicated in onset of ME/CFS more than other immunisations [25]. A study in 1936 by Gilliam et al described the inoculation with a polio vaccine of 458 people with lead to local reactions (i.e. at the site of the vaccination), general reactions in 17 people (3.7%) of which, very serious reactions were reported in 4 patients (0.9%). The latter 4 patients suffered loss of consciousness, onset of pain the knees, weight loss and rheumatism. [26]. Over 70 years later and after further unfavourable studies, serious adverse reactions continue to be reported with the polio vaccine. A report about a vaccine-related polio outbreak in Nigeria appeared on the BBC web site in October 2007 [27].

‘The WHO says the outbreak occurred when some of those who had received the oral polio vaccine excreted a mutated form of the virus which infected those who were not immunised.’

One recent paper strongly established a high rate of EV infection of the stomach of an ME/CFS patient cohort. [28] Muscle biopsy studies for EV infections in other patient cohorts have given mixed results and have lead other authors to conclude that further evidence is needed to see how the Chia study fits in with existing work on ME/CFS. [29] Such discrepancies no doubt relate to patient selection, which is largely based on broad definitions of ME/CFS and continues to cause difficulties in correlating one study of ME/CFS-labelled patients with another.

Adverse events in ME/CFS, GWS and Multiple Sclerosis (MS) patients have also been reported with Hepatitis B vaccines and anthrax. [30-33]. Nicolson et al have extensively studied the adverse events occurring in ME/CFS and GWS. [32] Even Prof. Simon Wessely has admitted, according to an attendee’s report of a lecture that he gave at Gresham College, London during January 2006, that some evidence had been found linking both the type and the quantity of vaccines administered to Gulf War soldiers with illness. In particular, that the combination of the anthrax vaccines and pertussis (Whooping Cough) given to soldiers was ‘suspect’. [33]

It would appear that the action of a vaccine in precipitating some cases of ME/CFS and related conditions (GWS) may be due to the contents of the adjuvant (which often includes aluminium), the main pathogen itself the subsequent development of a mutated ‘replacement’ pathogen, the preservative (e.g. mercury) or a combination of all of these factors.

Recently by Dietert et al postulated that chronic diseases including ME/CFS may develop later on in life after an ‘early life insult’. This hypothesis considers the possibility that foetal and early life exposure to ‘environmental toxins, maternally-administered drugs, infections or from postnatal exposure to toxicants, infectious agents and allergens’ can lead to Developmental Immunotoxicity (DIT). This causes various immune abnormalities relating to T-cell function, exaggeration of cytokine and inflammation responses as well as damage to the neurological and cardiovascular systems, endocrine and reproductive organs. [34] However, Dietert’s hypothesis is that in ME/CFS patients, DIT leads to changes to the immune system and a resulting aberrant immune response rather than aggravation of underlying mitochondrial disorders and subsequent exercise intolerance. [35] This is not necessarily in agreement with other studies of mitochondrial dysfunction of ME/CFS patients as outlined below. These mitochondrial studies seem to have more in common with those carried out on Autism/ASD patients than the studies of ME/CFS patients covering faulty immune responses with the major theme of ‘abnormal immune responses’ to otherwise common infections and toxins found in the everyday environment.

Mitochondria/ATP Dysfunction

There are extensive studies of mitochondrial dysfunction in ME/CFS-labelled patients. The UK physician, Dr Melvin Ramsay, who first used the term Myalgic Encephalomyelitis (ME) made a study with, Dr Alan Rundle, consultant pathologist at St Lawrence’s Hospital, Caterham, Surrey, UK published a study in the Postgraduate Medical Journal of December 1979. The study looked at blood levels of serum myoglobin and various enzymes that showed a similar biochemical pattern to Duchenne Muscular Dystrophy (a genetically inherited neurodegenerative disease). Interestingly, Ramsay and Rundle found no increase in Creatine Phosphokinase (CPK) in any of the patients but they did find high serum myoglobin (indicative of muscle damage) and raised serum glutamic oxaloacetic transaminase (GOT) mitochondrial (and cytosolic) enzyme which is normally present in heart, liver and other tissues. Raised serum GOT levels are suggestive of damage to the cells in these organs. Ramsay went on to conclude that the aetiological factor in ME could be causing loss of intracellular energy and permeability of muscle cells, leading to differential loss of intracellular proteins. [36]

In 1991, Behan et al carried out muscle biopsies on 50 patients diagnosed with ‘Post-Viral Fatigue Syndrome’ (PVFS) and found mild to severe atrophy of type II fibres in 39 biopsies, with a mild to moderate excess of lipid. 35 patients showed branching and fusion of mitochondrial cristae and mitochondrial degeneration in 40 of the biopsies with swelling, vacuolation, myelin figures and secondary lysosomes. [37]

In 1998, Lane et al studied an ME/CFS patient cohort and found that some patients:

‘showed a significantly lower ATP synthesis rate during recovery [from exercise]….indicating impaired mitochondrial oxidative phosphorylation.’ [38]

Lane made it clear in this publication that such abnormalities were not due to inactivity or deconditioning. Later Fulle et al discovered a fault in the mitochondrial membrane affecting calcium ion-transport and postulated that it could be causing the post-exertional symptoms in ME/CFS patients. [39] Muscle biopsy studies carried out by Pizzigallo et al showed morphological, biochemical and molecular ‘alterations’ in ME/CFS diagnosed patients. [40] Specific abnormalities included changes in mt-DNA, reduction of cytochrome-oxydase and citrate-synthetase enzyme activities and muscle fibre hypertrophy.

Under a section in his paper entitled ‘Chronic Fatigue’, Chinnery et al [18] suggests testing creatine kinase, fasting lactate or electromyogram to determine whether a mitochondrial myopathy has been ‘misdiagnosed’ as CFS. However, he concedes that normal results for these tests would not be reliable enough to rule out such a condition.

Nicolson and Ellithorpe [41] state that the high level of production of Reactive Oxygen Specied (ROS) and Reactive Nitrogen Species (RNS) causes damage to the mitochondria’s electron transport chain in ME/CFS-labelled patients. Normally this type of damage would be seen with aging but is seen prematurely in ME/CFS due to excessive levels of ROS and RNS which cause intracellular damage to mitochondria and loss of OXPHOS activity. (a similar conclusion to that of Ramsay and Rundle in 1978). Such damage if not constantly repaired, may lead to genetic damage to mitochondria (mutations and deletions).

Infections are known to cause oxidative stress regardless of any underlying genetic predisposition, and may account for the epidemic occurrence of ME/CFS. The concept of ‘mito-pathogens’ (mitoviruses, mitoviroids and mitobacteria) with a particular toxicity towards mitochondria have been proposed [42]. In addition some pathogens are ‘energy parasites’ and rapidly use ATP made by the mitochondria because they are unable to make their own. Examples include Chlamydia Pneumonaie (CPN), Rickettsial pathogens and certain viruses. [43, 44, 45] The action of these mito-pathogens in creating oxidative stress and/or fast use of ATP may account for epidemics and sporadic fast onset of disease in many ME/CFS-labelled patients and to distinguish this patient population from those suffering a slower progression of fatigue caused by a more prolonged effect of milder oxidative stress. The possibility that this effect is amplified in persons who have suffered an ‘Early Life Insult’ such as a vaccine or other environmental exposure may interplay with exposure to mito-pathogens and/or energy parasites. There is a range of possibilities here in terms of the nature of toxins, infections, genetics, rate and age of onset that may account for subsets of sufferers with different disease patterns placed collectively under the label of ME/CFS. The unifying factor however is an ‘exercise intolerance’ and associated markers of metabolic disturbance, which as these discussions have shown, can arise due to different malfunctions in Cell Respiration and this can be evidenced by measurement of ATP production, use and recycle (see below section on Tests).

Various groups have carried out gene expression studies on ME/CFS-labelled patients and have uncovered evidence of both mitochondrial dysfunction and neurodegeneration. Kerr et al have established an upregulation of a gene known as ‘neuropathy target esterase’ (NTE) which is a target for organophosphates and chemical warfare agents. [46] These chemicals have been postulated to have caused at least some of the symptoms of Gulf War Syndrome (GWS). Kerr also found upregulation of EIF2B4 (eukaryotic translation initiation factor 2B, subunit 4 delta, 67kDa), EIF4G1 (eukaryotic translation initiation factor 4 gamma, 1) and MRP123 (Mitochondrial Ribosomal Protein 123). These genes are involved in the protein synthesis aspects of mitochondrial function. In Hannah Poling’s case, her mitochondrial genetic mutation was considered more likely to cause problems because, according to the New York ASD researcher Dr Salvatore DiMauro, the gene is pivotal to protein production and that in Hannah’s case it would be important to show that protein synthesis was inhibited as this was likely to have a *‘huge impact on other mitochondrial genes and energy production by cells’.* [5]

Kerr et al published a new study in 2007 with detailed results of the gene expression of 55 ME/CFS patients. [47] In this moderate sized patient cohort, selected using the Fukuda criteria, a large array of different genes, 88 in total, were found to be up or downregulated. The results allowed 7 different sub-types of patients to be identified. Further studies are to be undertaken but 5 of the gene expression markers (APP, CXCR4, FNTA, IL6ST and TNFRSF1A) have been highlighted as areas where existing drugs could be trialled. (e.g. ‘anti-TNF’ drugs including etanercept). The highest rate of upregulation amongst these 5 genes is

~5-fold for IL6ST in sub-type 7. However, the rate of upregulation of some of the other genes is considerably higher e.g. GA-binding protein transcription factor - GABPA (23.28-fold and 15.56-fold in Sub-types 2 and 3 respectively) and Mitochondrial Ribosomal Recycling Factor - MRRF (28.27-fold and 38.4-fold in sub-types 1 and 2 respectively).

GABPA, according to the OMIM database contributes to the transcriptional regulation of a number of subunits of mitochondrial enzymes, including cytochrome c oxidase and mitochondrial transcription factor. Therefore the two genes with the highest fold upregulation in the Kerr study are related to the functioning of the mitochondria. Presumably the drug trials referred to in this study have applicability to only some of the symptoms and in a certain percentage of the ME/CFS patient community. It appears that new drugs and treatments may have to be developed to address some of the other upregulated genes.

It should be noted however that quantitative measurement of mitochondrial gene expression is not the same as measurement of mitochondrial gene mutations/deletions. The latter are inherited or developed over time due to environmental influences and ageing and can be measured by analysing genomic DNA in human cells. Gene expression in contrast is the behaviour of genes at any given time (i.e. the chemicals expressed by them) and this may or may not result from defective DNA. As a diagnostic, the gene expression profiling may turn out to be useful especially if applied to patients meeting neurological criteria for ME/CFS but they will not establish whether a primary inherited mitochondrial dysfunction is present or whether it is causing a problem with the use, recycle or supply/demand of ATP. Other tests have been developed and are commercially available, which look directly at faulty energy production processes in the mitochondria. (See below section on Tests). Utilisation of these available tests may be very useful for helping to establish that ME/CFS has been correctly diagnosed and relates to the cardinal feature of ‘exercise intolerance’ as outlined in both the Ramsay criteria and Canadian Guidelines. [36, 48]

Testing

The studies outlined within this document were not included in the York Systematic Review and therefore were not considered in the formulation of the CFS/ME NICE Guidelines. Furthermore, the test panel recommended by the Guidelines does not include any need to test for nutritional status, immune or endocrine status, no cardiac testing, imaging (MRI, SPECT), metabolic testing or muscle biopsy. (See Fig. 5) Nothing in the test list could be used to adequately assess mitochondrial dysfunction, ATP status or neurodegeneration. Serum Creatinine and Creatine Kinase (CK) have been found to be normal in ME/CFS-labelled patients by key researchers including Ramsay and Chinnery even when other signs and symptoms of mitochondrial disease/dysfunction were present. [18, 36] These tests if normal, cannot be regarded as exclusionary for mitochondrial dysfunction or as a reason to decline further testing.

In many instances patients turn to private testing to elucidate the abnormalities in their cases and access appropriate healthcare at their own expense. That patients are able to find abnormal test results when NICE assure doctors that if the recommended panel is negative, nothing further is necessary, is proof alone that the Guidelines on diagnosis are invalid if not dangerous. These are some of the pivotal reasons why the NICE Guidelines for CFS/ME are being challenged via the One Click Judicial Review.

Various companies offer tests for metabolic and mitochondrial dysfunction. These range from relatively simple blood tests for certain markers e.g. mitochondrial antibodies, mitochondrial myopathy, CoEnzymeQ10 levels, creatinine, Creatine Kinase, ALT (Alanine Aminotransferase), alkaline phosphatase iso-enzyme. Other companies offer tests that look directly at faults in the mitochondrial or nuclear genome. Muscle biopsies may be necessary for some of these tests. A compilation of companies advertising such tests is given in

Appendix 1. These companies have not been vetted by the author and are given for information purposes only.

Fig. 5 The NICE CFS/ME Guidelines (2007) Diagnostic Test Panel:

- Urinalysis for protein, blood and glucose
- Full blood count
- Urea and electrolytes
- Liver function
- Thyroid function
- Erythrocyte sedimentation rate or plasma viscosity
- C-reactive protein
- Random blood glucose
- Serum creatinine
- Screening blood tests for gluten sensitivity
- Serum calcium
- Creatine kinase
- Assessment of serum ferritin levels (children and young people only).

Specific tests NOT recommended:

- Tests for serum ferritin in adults….unless a full blood count and other haematological indices suggest iron deficiency.
- Tests for vitamin B12 deficiency and folate levels….unless a full blood count and mean cell volume show a macrocytosis
- the head-up tilt test
- auditory brainstem responses
- electrodermal conductivity.
- Serological testing unless the history is indicative of an infection.

Source: NICE CFS/ME Full Guidelines
http://www.nice.org.uk/CG53

A particular testing profile for ATP and mitochondrial dysfunction has been available in the private sector for some years now. Dr John McClaren Howard, the former Laboratory Director of Biolab UK in London, developed this ‘ATP profile’ which looks at several parts of mitochondrial function including ATP production, recycle and presence of toxins. These tests were commercially available from Biolab UK in London up until Dr McClaren-Howard’s retirement from Biolab in 2007. He now offers the tests through a new company called ‘Acumen’ based in the South West of England, UK. A GP referral is essential in order to be able to access the tests. There are various companies who offer genetic testing too, however it should be noted that these are very expensive, and to cover all possibilities could cost in the order of thousands of pounds.

Through various practitioners, a considerable number of ME/CFS-labelled patients and sufferers of Lyme Borreliosis and other tick-borne diseases (TBD) have had these tests. It was found that many were suffering severe difficulties with one or more parts of the ATP production process. Some were found to have heavy metals and other toxins bound to sites on the mitochondria which prevented the ‘raw materials’ for ATP production from entering the mitochondrial cell and being converted to energy. A patient advocate, Craig Robinson who collected and analysed these ATP results, found a high correlation with the level of patient disability as reported in his excellent Citizen’s paper. [49]

Treatments

Care must be taken in prescribing treatments to those with mitochondrial or metabolic disease and dysfunctions and subsequent poor ATP production. Several reports of adverse events and fatalities of drugs including amitriptyline, Prozac and statins have appeared in patients with these conditions. [50-54]. In some cases, the symptoms (e.g. cardiomyopathy) resolved upon cessation of the treatment and avoided the patient having to undergo major heart surgery.

Exercise intolerance is a key feature of the majority of metabolic and mitochondrial diseases and it is extremely difficult to see therefore how Graded Exercise Therapy (GET) can be regarded as an appropriate therapy. Several patient surveys to date highlight that it made the majority feel worse or no better and this is also evidenced by the high drop out rate in some controlled trials of GET. Administration of GET in patients with potentially undiagnosed and severe mitochondrial dysfunction would appear nothing short of negligent.

A number of practitioners have treated patients labelled with ME/CFS, MS, GWS and other neurological conditions with ‘mitochondrial supports’, e.g. D-ribose, alpha-lipoic acid, Acetyl-L-carnitine, CoEnzymeQ10, Vitamins B, C, NADH, pyruvate, creatine phosphate, Magnesium etc. [55] Anecdotally many patients report a benefit from such regimens, although they generally need to be on-going, with benefits disappearing if treatments are ceased. The benefit of such supplement protocols varies from person to person, and this may be due to the particular dysfunction in the metabolic pathways or mitochondria e.g. whether the correct enzymes are available to complete the complex chain of biochemical reactions involved in the process of cell respiration. In patients who find less benefit than others it could be the case that they are still lacking the ability to complete each stage necessary for ATP production, use and recycle and tests as outlined below may help to find out why.

Conclusions

This paper has highlighted the fact that metabolic/mitochondrial dysfunction (inherited and/or environmentally precipitated) have been found to be present in Autism/ASD, SIDS, GWS, neurodegenerative diseases, cancer, heart disease, diabetes and ME/CFS-labelled patients. These abnormalities are in other words widespread and are far from being the rare problem that government would have us believe. Such a finding cannot be downplayed or swept aside. It is now imperative that the momentum is not lost on further establishing the links between such disorders and the potential for vaccines, infections or other environmental toxins to precipitate, aggravate or even cause them. Further testing and study is necessary to find out more. Longer-term research would be welcomed but in the short term available tests such as muscle biopsies, blood tests, genomic profiling and the ATP Profile offered by Acumen may be key ways to establish faults in a patient’s energy metabolism. These tests may allow patients to establish whether there is a specific genetic and/or environmental factor causing the metabolic/mitochondrial dysfunction and to tailor his/her treatment to the specific problem. Once this information has been compiled on a large scale, we may be able to gain better recognition for these illnesses and start to look for therapies that may successfully treat the symptoms. The weight of this evidence as it grows will no longer be able to be ignored and those in power must take responsibility for past mistakes and prevent future ones.

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APPENDIX 1 LINKS TO RELEVANT ORGANISATIONS

Please note that the organisations listed below have not been vetted by the author and are provided for information only.

TESTING

Acumen Laboratory. Based in Devon, UK. CFS profile incorporating ATP, DNA, SODASE, Profile, Translocator Studies and others. These tests are relatively affordable compared with many of the others with the CFS profile costing ~£125. The service extends internationally.

Acumen Laboratory has no web site currently but can be contacted directly via email at acumenlab@hotmail.co.uk or telephone on +44 (0)7707 877175. Postal address is Acumen, PO Box 129, Tiverton, Devon EX16 0AJ, UK.

Biolab.UK – Based in London, UK. Offers a range of nutritional, biochemical, toxins testing.
www.biolab.co.uk
Genetic testing profile available from some consultants. Many familiar with the Acumen ATP profiles that were developed originally at Biolab.

Cigna – Offices in Broomfield, CT and Philadelphia, PA in the USA. Offers range of genetic testing including for mitochondrial disorders.
http://www.cigna.com

Cleveland Clinic, Cleveland, OH USA. Offers Genetic DNA and mitochondrial disease testing.
www.clevelandclinic.org

DNA WorldWide, Based in Surrey, UK. Offers International Service.
http://www.dna-worldwide.com

Gendia Based in Belgium. – Hundreds of tests by gene and disease including ‘exercise intolerance’ and SIDS. Links to the OMIM Database
www.gendia.net

Genetests – An online database of institutions performing Genetic Testing funded by the National Institute of Health (NIH)
www.genetests.org

Medichecks list contains tests for mitochondrial antibodies, mitochondrial myopathy, CoEnzymeQ10, creatinine, Creatine Kinase, ALT (Alanine Aminotransferase), alkaline phosphatase iso-enzymes and various others that could be used to test for mitochondrial dysfunction. The full list of tests is available on their web site and specific genetic tests listed under the second URL shown below.

www.medichecks.co.uk
http://www.medichecks.com/Genetic_tests.cfm

MitoSciences. Based in Eugene, Oregon, USA, Not clear whether it offers individual testing, or kits just for clinical R&D. Interesting info on mitochondrial disorders on the web site.
http://www.mitosciences.com

The Doctor’s Laboratory. Located in London, UK. Offers a wide range of tests including general biochemistry, vitamins, minerals, pathogens of all types, some genetic testing. Tests from TDL can also be offered via Medichecks.
www.tdlpathology.net

CHARITIES & ORGANISATIONS

The Children's Mitochondrial Disease Network
http://www.emdn-mitonet.co.uk/

British Society for Human Genetics
http://www.bshg.org.uk/

EUMitoCombat
http://www.eumitocombat.org/index2.php

Mitolinks UK
http://www.communigate.co.uk/ne/mitolinks/

MitoMatters UK
http://www.mito-matters.org.uk/?page_id=17

Mitochondrial Research Society
http://www.mitoresearch.org/

Society For Inherited Metabolic Disorders (SIMD)
http://www.simd.org/

The Genetic Interest Group (GIG)
http://www.gig.org.uk/

United Mitochondrial Disease Foundation (UMDF)
www.umdf.org