

The Aerobic Energy Production and the Lactic Acid Excretion are both Impeded in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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Abstract

Background: In this study the muscle bioenergetic function in response to exercise in severe ME was explored to see if the underlying metabolic problem in ME, responsible for the severe difficulties with trivial exercise, and the severe loss of muscle power, could be discovered.

Methods: Inorganic phosphate, creatine kinase and lactate were measured in a former Dutch National Field Hockey Champion, who is now a patient bedridden with severe ME, before and 5 minutes after very trivial "exercise", from which his muscles needed 12 hours to recover.

Results: Inorganic phosphate and creatine kinase were both normal, however, lactate after this trivial exercise was very high, and further testing showed that a second batch of lactic acid was excreted after the same exercise with a 6-fold delay, showing that the lactic acid excretion was impaired and split into two. And this was delayed up to 11- fold by eating closer to the exercise.

Conclusion: This study found that in severe ME, both the oxidative phosphorylation and the lactic acid excretion are impaired, and the combination of these two is responsible for the main characteristic of ME, the abnormally delayed muscle recovery after doing trivial things. The muscle recovery is further delayed by immune changes, including intracellular immune dysfunctions, and by lengthened and accentuated oxidative stress, but also by exercise metabolites, which work on the sensitive receptors in the dorsal root ganglions, which in severe ME are chronically inflamed, and are therefore much more sensitive to these metabolites, which are produced in high quantities in response to trivial exercise, which for ME patients, due to the underlining metabolic problem, is strenuous exercise. And a similar problem is most likely responsible for the abnormally delayed brain recovery after doing trivial things.

This study also shows that the two metabolic problems are the result of an impaired oxygen uptake into the muscle cells or their mitochondria and in combination with the Norwegian Rituximab studies, which suggest that ME is an autoimmune disease, it is suggestive that antibodies are directly or indirectly blocking the oxygen uptake into the muscle cells or their mitochondria.

Keywords: Myalgic encephalomyelitis; Chronic fatigue syndrome; Exercise; Muscle fatigue; Muscle pain; Lactate; Lactic acid; Immune dysfunction; Inorganic phosphate; Creatine kinase

Abbreviations

ME: Myalgic Encephalomyelitis; CFS: Chronic Fatigue Syndrome; ME/CFS: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; PEM: Post Exertional Malaise; Pi: Inorganic Phosphate; CK: Creatine Kinase; ATP: Adenosine Triphosphate; ADP: Adenosine diphosphate; GET: Graded Exercise Therapy; CBT: Cognitive Behavioral Therapy; DRG: Dorsal Root Ganglions

Background

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic multi-system disease that can lead to striking debilitation [1-3]. The pathophysiology is related to activation of immunoinflammatory pathways and autoimmune responses underpinned by a state of energy depletion [4] and elderly patients with ME/CFS are at increased risk for non-Hodgkin's lymphoma [5].

As reported by Jason et al. the median age of death for cancer in the United States is 72 versus an average age of 47.8 if the person also has ME/CFS and the average age of death of heart failure is 83.1 versus 58.7 years if the person also has ME/CFS [6]. What this means is that ME/CFS patients

who died of cancer or heart failure were considerable younger than what would have been expected from the general population, which means that ME/CFS increases the risk of death from these conditions dramatically [6], which constitutes indirect proof that ME/CFS is a physical disease.

A quarter of ME/CFS patients have severe ME/CFS, are homebound or bedridden and suffer major functional impairments [2,7] to the point that some are tube fed due to dysphagia and /or dysparexia of the stomach caused by autonomic dysfunction which is a frequent finding in ME/CFS [8].

Patients with severe ME are bedridden because of a lack of muscle power, not because they are tired, yet hardly any research is done on patients with severe ME to find out why they are so severely disabled.

ME and CFS are often used interchangeably, even though the case criteria for ME and CFS define two distinct, partially overlapping diseases [9], which have different cytokine profiles [10].

The diagnosis ME requires both M and E problems, whereby M stands for Myalgic i.e. muscle pain and muscle energy production problems and E for Encephalomyelitis, i.e. specific neurological, neuroimmune and neurocognitive problems.

The main characteristic of ME is an abnormally delayed muscle recovery after doing trivial things [11], as witnessed and documented by infectious disease specialist Dr Melvin Ramsay after the 1955 outbreak of an unknown disease in the Royal Free Hospital in London [11] which at first was thought to be an atypical form of poliomyelitis [11] and later became known as ME. Dr Ramsay also documented that the diagnosis of ME should not be made in the absence of an abnormally delayed muscle recovery after doing trivial things [11].

This complaint of delayed muscle recovery from fatiguing exercise in ME/CFS was confirmed and objectified by Paul et al. who let patients and sedentary controls carry out a fatiguing exercise test with their quadriceps muscles and found a big difference in muscle recovery time [12].

These days the distinctive feature of ME is often referred to as “post-exertional malaise” (PEM), and encompasses disabling and persistent muscle and/or brain fatigue following minimal exertion, usually accompanied by increases in symptoms in general, and muscle and/or brain symptoms in particular, including cognitive dysfunction [1,2,9]. VanNess et al. found that PEM in ME/CFS is incapacitating and that ME/CFS patients responses to exercise are distinctively different from those of sedentary controls who are deconditioned because they do not like or want to do exercise contrary to ME/CFS patients who are very keen to exercise but are unable to because of an underlying metabolic problem [13].

Other common ME/CFS symptoms include, but are not limited to, sleep disturbance, pain, and symptoms associated with autonomic dysfunction such as orthostatic intolerance, postural orthostatic tachycardia syndrome (POTS), light and sound hypersensitivity, dizziness, tinnitus, severe headaches and/or gastrointestinal disturbances. Muscle and/or brain fatigue in ME are not alleviated by rest and may be exacerbated by physical or cognitive activity [1,2]. The more muscle and/or brain power you lose, the longer the recovery periods become. In my case if I walk the 5 to 6 yards to the toilet and back, it takes 12 hours before I have enough muscle power to walk the same trivial distance again.

A minimal increase in a ME patient's typical level of activity, has a dramatic negative impact on the ability to carry out both physical and cognitive activities of daily living [1,2]. In other words if you go over your limit you get a relapse and the bigger the relapse the less likely you are to recover from it. Whereby the severity of the symptom flare after moderate exercise is linked to cytokine activity [14].

I developed ME after picking up pneumonia from a patient, who coughed me in the face, and during the first few weeks of falling ill with ME, my legs needed 15 minutes to recover from walking 20 to 30 yards, before I could walk the same trivial distance again, which illustrates the abnormally long periods of rest to recover from minimal exertion. In the days before I developed ME, walking that distance was easy, even though I was still recovering from pneumonia, coughing a lot and still on antibiotics. So suddenly, from one day to the next, I lost about 70-80% of power in my legs, about 50-60% of power in my arms, I began to suffer from severe dizziness, I started to have daily headaches, from which I had never previously suffered, and I started to have problems sleeping for no reason, which I never had before either. The problems with walking were even stranger because I looked well, I didn't feel ill and before the pneumonia I was fit and well, I was hardly ever sick and shortly before I fell ill with pneumonia, I was running 3-4 times a week, with a long run of 20 to 25 km on Sundays and I do not smoke and hardly ever drink alcohol.

Before acquiring the illness most patients were healthy, leading full active lifestyles and ME/CFS most frequently follows an acute pro-dromal infection, often a respiratory infection or an acute “flu-like” illness [2]. And I'm a good example of both. I love sports and amongst things I am a former Dutch national field hockey champion, captain of my team.

The distinctive feature of CFS [9,15] on the other hand is chronic fatigue which must have lasted for 6 months or more, which is unexplained and needs to be accompanied by at least four out of eight symptoms, e.g. sore throat, unrefreshing sleep, and headaches. While post-exertional malaise is not obligatory for CFS [9,15], (chronic) fatigue is not mandatory for the diagnosis of ME [9,15].

Exercise intolerance is a cardinal feature in ME and various high quality studies found decreased physiological exercise capacity in individuals with ME/CFS [1,8,12-16] and using novel magnetic resonance techniques Jones et al. identified a distinctive, reproducible muscle bioenergetic abnormality in patients with ME/CFS [8], the degree of which not only associates with autonomic dysfunction, found in the majority of ME/CFS patients [8] but also with a characteristic cardiac bioenergetic impairment [17].

Various studies have observed impaired skeletal muscle metabolism in ME/CFS [15], acidosis during exercise, taking 4 times longer for the pH to go back to normal in ME/CFS [8, 16] and acidosis inhibits oxidative phosphorylation in contracting human skeletal muscle [18].

Wong et al. found low intracellular concentrations of ATP [19], confirming that the impaired physical activity in ME/CFS compared to healthy controls is related to a bioenergetic muscle abnormality which makes moderate and vigorous activity almost impossible and if it gets worse patients lose the muscle strength or power to sit, stand or walk and therefore they become bedbound with severe ME.

As noted by Morris et al. many studies have demonstrated a significant positive correlation between markers of inflammation and symptom severity [4]. And a rapid decline of inflammation in patients corresponded with a decline in severity of fatigue and amelioration of their entire symptom profile [4]. Markers of chronic inflammation have also been detected in skeletal muscle and correlate with objective measures of muscle fatigability [4].

Energy for skeletal muscle contraction is supplied by anaerobic and aerobic metabolic pathways. The aerobic system is the most efficient energy source, producing up to 18 times more energy in the form of ATP than if glucose was used anaerobically. But the downside of the aerobic system is that without oxygen it doesn't function [20].

The glycolysis is the anaerobic metabolic pathway to produce ATP, used for bursts of all-out exercise lasting from 60 to about 90 seconds as reported by De Feo et al. [21], and is a very fast way to produce energy. During glycolysis, carbohydrate, in the form of either glucose or glycogen, the stored form of glucose, is broken down through a series of chemical reactions ultimately forming lactate. Very little energy is produced this way, but the trade-off is that you get the energy very quickly if oxygen demand outstrips oxygen supply [20,21].

The other problem of the anaerobic glycolysis is an increase in hydrogen ions and lactate, which causes muscle acidosis, and the production of metabolites in the form of ADP, Pi and potassium ions [21-23]. Acidosis and the accumulation of these metabolites cause a number of problems inside the muscles, including inhibition of specific enzymes involved in the anaerobic glycolysis and in muscle contraction leading to a very rapid loss of muscle power, i.e. within 1 to 2 minutes, with concomitant quickly increasing muscle pain [18,20-23] to the point that after 1 to 2 minutes of anaerobic exercising, one can hardly stand on one's legs anymore. And this is exactly what happens if I walk the trivial distance of 5 to 6 yards to the toilet and back. And the longer I need to sit on the toilet, the longer it takes me to complete this trivial exercise, the more muscle power I lose and the more muscle pain I've got.

There has been substantial research to show that a build-up of acid within muscle or plasma is one of the factors which causes fatigue [25]

and artificially induced acidosis can impair muscle contractility even in non-fatigued humans [26].

A number of papers have challenged this model to explain muscle fatigue. In place of acidosis it may be that inorganic phosphate is a major cause of muscle fatigue [27] which is produced during the breakdown of ATP to ADP. However, there are several limitations regarding this phosphate hypothesis, one of them is that loading of acid neutralizing agents, when ingested shortly before high intensity exercise, means one can go faster or further [28], which was one of the reasons why Robergs et al. [23] concluded that increased lactate concentration remains a good marker for the onset of fatigue.

The pain and symptoms in my legs after a trivial walk feel very similar, albeit a lot worse, to the muscle symptoms I had in the past after a very strenuous training, and the objective therefore was to try and identify the underlying bioenergetic muscle problem in ME, responsible for the exercise intolerance, rapid muscle fatigue and delayed muscle recovery.

The study by Byrne et al. [29] showed that skeletal muscle carnitine, phosphorylase, all glycolytic enzymes and the mitochondrial marker enzymes monoamine oxidase, isocitrate dehydrogenase and cytochrome oxidase were normal. They therefore concluded that there was no major intrinsic defect in the muscle energy pathways in ME/CFS [29].

Edwards not only noted that muscle fatigue and pain occurring at rest without any exercise, suggests it is psychological in origin but also that if it happens or gets worse after exercise, as is the case in ME, it's indicative of a muscular problem [30]. Exercise fatigue or pain should ideally be reproduced by an appropriate provoking exercise test and plasma creatine kinase and lactate are specific indicators of a muscular cause [30].

I hypothesized that I might be able to come up with the bioenergetic reason for my muscle problems by measuring my inorganic phosphate, creatine kinase and lactate before and after exercise, as it's clear from the literature and my symptoms, that there is a major bioenergetic problem responsible for my severe loss of muscle power and the very long muscle recovery times after trivial walks.

Successfully identifying the underlying metabolic problem in ME/CFS would make it easier for doctors to diagnose the disease and prevent symptom exacerbation or relapses from exercise regimes of which patients have been complaining for a long time and which was objectified by a graded exercise trial by Black et al. [31] but also by a recent large survey by the British ME Association which concluded and asked for the immediate withdrawal of harmful Graded Exercise Therapy (GET) as a treatment for ME/CFS [32].

Methods

Participants

The participant, i.e. the writer of this article, i.e. me, is a patient who has been bedridden with severe ME for more than 10 years, after Graded Exercise Therapy caused a severe relapse from which I haven't recovered so far. I was diagnosed with ME by 2 knowledgeable primary care physicians who in the absence of a diagnostic test for ME/CFS, used the 1994 Fukuda [33] and the Canadian Consensus Criteria [34] to diagnose the disease, and the diagnosis was later confirmed by a consultant neurologist and by using the International Consensus Criteria [2].

Prior to falling ill with pneumonia, which triggered my ME, I was fit and well, was hardly ever ill and was very sporty. I do not smoke, and hardly ever drink alcohol. I have a brown belt in judo; I'm a former Dutch national field hockey champion, captain of my team; I ran marathons (PB: 3.05), half marathons (PB: 1.19), and competed in quarter triathlons.

I do not have a history of an autoimmune disorder, MS, psychosis,

major depression, heart disease, thyroid-related disorders or any other chronic illnesses apart from ME, I had a very happy childhood, no childhood traumas, I'm not a perfectionist, I do not suffer from anxieties, mental health problems were excluded by a consultant psychiatrist and there are no confounding factors influencing my ME.

I do however have allergic rhinitis and hay fever, which has become a lot worse since I have got this disease, and research by Yang et al. shows that people with allergies have a 64% increased risk to develop ME/CFS [35] which provides another clue that ME/CFS might be an autoimmune disease [7].

In order to establish base line levels, my creatine kinase, inorganic phosphate and lactate were measured 1 minute before the exercise, consisting of walking the 5 to 6 yards from my bed to the toilet, sitting on the toilet, standing up, taking one step to the right, washing my hands and walking the 5 to 6 yards back to my bed.

Blood lactate concentrations peak about 5 minutes after the cessation of intense exercise [36], the delay is attributed to the time required to buffer and transport lactic acid from the tissue to the blood [37], and therefore my creatine kinase, inorganic phosphate and lactate were all measured 5 minutes after the exercise.

Blood sample collection occurred via a finger prick, using pediatric sized tubes, the blood was then centrifuged and samples were sent via overnight express to the head of the Deventer Hospital Laboratory in the Netherlands, who is also one of the founders and directors of Hessels+Grob bv who supplied the finger prick lancets in a small ready to use, disposable plastic device, the pediatric size tubes, the centrifuge etc to enable blood taking in a very simple way, so that the samples could be analyzed the next day, although centrifuging meant that the laboratory had 5 days after the blood was taken to do the measurements/analysis. By using finger pricks and pediatric sized tubes, one only needs 4-5 drops of blood per tube.

Statistical analysis

Statistical analysis was performed by Statisticor, a Dutch independent firm for statistical analysis.

Medical ethics

The research protocol was discussed with the Centrale Commissie Mensgebonden Onderzoek (CCMO), the Dutch Government Human Research Ethics Committee, and they concluded that for this particular form of research, approval from a Human Research Ethics Committee was not required.

Results (Table 1)

In this study creatine kinase (CK), inorganic phosphate (Pi) and lactate were measured before and after exercise in a patient with severe ME. As seen in Table 1, my CK and Pi were normal before and after exercise. The CK levels can rise and reach a maximum 4 days after the exercise [38]. In my case as I have been doing the same exercise twice a day for the last few years, it means that the measured CK levels are also the CK levels 1, 2, 3, and 4 days after the previous exercise [38]. The normal CK levels indicate that there is no sign of muscle damage and the normal inorganic phosphate means that inorganic phosphate is not responsible for the delayed muscle recovery.

As expected my lactate was normal before the exercise but it was abnormal at 8.0 at the 5 minute point. Most healthy people, including most healthy ordinary sports people, will stop exercising, as your legs become very heavy, (well) before they reach the 8 mmol mark because from that point onwards they will experience muscle pain due to the buildup of lactic acid etcetera.

Patient with severe ME	1 minute before the exercise	5 minutes after the exercise	30 minutes after the exercise	Std. Deviation	
Creatine kinase (CK)	96	110	—	9.90	N= - 200 U/l
Inorganic phosphate (Pi)	1.45	1.15	—	0.21	N= 0.90 - 1.50 mmol/l
Lactic acid	1.6	8.0	11.8	5.15	N= - 2.2 mmol/l

Table 1: Creatine kinase, inorganic phosphate and lactic acid before and after trivial exercise in severe ME.

Normally, one should be able to do this trivial walk aerobically, only producing a tiny amount of lactic acid when getting up from the bed and getting up from the toilet.

My elevated lactate at the 5 minute mark confirmed my theory that my muscles were having an energy problem, so the next questions were why my muscle symptoms go away doesn't and why is there a noticeable 30% reduction in pain around the 30 minute mark? Therefore it was decided to check my lactate levels much more often using a hand held lactate tester to find out what happened with my lactate levels.

Recently Bonaventura et al. published a study in which they compared six hand-held blood lactate analyzers to a golden standard laboratory analyzer [39]. All six demonstrated accuracy and reliability but the test winner was The Edge, which performed best below but also above 15 mmol. Therefore it was decided to use The Edge for further lactate testing to analyze blood samples obtained from the fingertip.

Many sports physicians and exercise physiologists advice to check the maximum blood lactate levels 5 minutes after finishing a maximum exercise as found by Gollnick et al. [36]. Other research teams found that the maximum lactate level after maximum exercise was reached at 4 to 6 minutes [40], 3 to 8 minutes [41] and 6 to 9 minutes [42]. In my case checking it every minute with the handheld lactate analyzer confirmed that I reach my maximum 5 minutes after maximum exercise as found by Gollnick et al. [36] and "predicted" by the sport Physician I consulted.

Testing with the lactate analyzer showed that the clearance of lactate from the blood worked fine and that around the 30 minute mark, I suddenly excrete a second batch of lactate i.e. 11.6 mmol/l, which means that my lactic acid excretion, contrary to normal, is split into 2 and that I not only produce 8.0 mmol/l at 5 mins but also 11.6 mmol/l at 30 mins just to be able to finish this trivial walk which for me is very strenuous exercise as highlighted by the high levels of lactate.

And that means that the lactic acid excretion by the muscle cells is impeded to the extent that a large amount of lactic acid is not only excreted around the 5 minute mark but also around the 30 minutes mark, whereby the largest amount of lactic acid is excreted around the 30 minutes mark. But it also means that a large quantity of lactic acid remains in the muscle much longer than normal.

This obviously has implications for my muscle recovery, my muscle pain etc. In addition, the longer the lactic acid stays in the muscle, the more the anaerobic energy production is blocked by the raised lactic acid levels and acidosis, causing loss of muscle power [18].

So the question is, what do these abnormal levels, following such a trivial walk, mean? The answer can be found when we go back to the very first day that I fell ill with this disease. Overnight, from one day to the other, I lost 70 to 80 % of power in my legs and suddenly, walking 15-30 yards was very far, and after that my legs felt very heavy and needed 15 minutes to recover before I could walk 15-30 yards again. This means that I had lost a lot of muscle power, power which is produced by the aerobic energy production. And when the aerobic energy production cannot meet the energy demand, the anaerobic energy production automatically kicks

in to help out. The consequence of that is the production of large amounts of lactate for exercise that one normally can do aerobically. And that is what happened on the very first day that I fell ill with ME, and has been happening ever since.

The only difference is that with every relapse I lose more aerobic power, and therefore the anaerobic energy production has to kick in earlier and earlier to help out. And that also means that the more the aerobic production becomes impeded, the less energy is produced. The less energy is produced, the more muscle power one loses and the sooner the anaerobic production has to help out and the more and the sooner lactic acid is produced, even though the activities become more trivial after each relapse. As soon as I finish the exercise, I have to lie down because I'm rapidly losing muscle power in my legs and at the same time I'm starting to get more and more muscle pain. It might sound strange but walking back and forth to the toilet is more difficult than running a marathon. However if you see my lactate levels of 8.0 mmol/l around the 5 minute mark, and 11.8 mmol/l around the 30 minutes mark, both produced by the same exercise, it means that the actual lactate production for this very trivial exercise is 19.8 mmol/l. That is a level that many professional athletes will never / not often reach and that sort of level of lactate makes it easy to understand why this trivial walk is so strenuous an exercise for me and more difficult than running a marathon. And it is therefore no wonder that I have severe loss of muscle power combined with severe muscle pain from this trivial walk to the toilet and back.

An Unexpected Finding

One evening I checked my lactate after exercise yet for some unknown reason the second peak of lactate in the blood, 30 minutes after exercise, didn't happen. The strange thing was that my legs remained very painful and the 30% reduction in pain, which normally happens at the 30 minute mark didn't happen either, and it took another 25 minutes before the noticeable 30% reduction in pain was there, this time at the 55 minute mark, whereby my lactate peaked at 9.4 mmol/l.

A few days later I checked my lactate after exercise again, which lasted about as long as the previous exercise, yet this time the lactate was only 8.1, and it was reached after 35 minutes instead of 55, again for no apparent reason, which obviously raised the question why was it not as usual at the 30 minutes mark and what is the main difference between the two episodes, responsible for this difference?

When the maximum lactate in the blood was reached after 55 minutes, I had my evening meal about one hour before the exercise and when it was reached after 35 minutes, I had it about 2 - 2 1/2 hours before the exercise.

It seems logical that if lactic acid stays longer in the muscle that this leads to increased acidity and a reduced pH, which then leads to more muscle fatigue and muscle pain. Something similar was described by Jones et al. [16] when they found that a large subgroup of ME patients exhibited a 4-fold increase of the time taken for the muscle pH to recover to baseline following exercise and the net effect of this is sustained exercise-induced acidosis in the muscle which has a significant impact on muscle function [16] and inhibits oxidative phosphorylation in contracting human skeletal

muscle [18] but also contributes significantly to the expression of muscle fatigue [16].

Discussion

In this study, I set out to explore the muscle bioenergetic function in severe ME to see if I could find out why ME patients have severe problems with exercise even though most of them were fit and well, very sporty and active before they fell ill with ME [2].

From the very first day I fell ill with this disease I lost a significant amount of muscle power and at the same time my muscles needed abnormally long to recover from walking trivial distances illustrated by the fact that in the beginning of this disease my legs needed 15 minutes to recover from walking 20 to 30 yards. Over time with every relapse the distance I can walk has become shorter, the recovery time has become longer and at the same time I get severe muscle pain from walking trivial distances.

In this study inorganic phosphate and creatine kinase measured before and after exercise were both found to be normal which shows that the inorganic phosphate is not involved in the delayed muscle recovery and the normal CK shows that there is no sign of muscle damage.

In this study abnormally high lactate levels 5 minutes after exercise were found but at the same time it was found that the lactic acid excretion was split into two and that a second large amount of lactic acid was excreted 30 minutes after exercise. It also showed that eating less than 3 hours before the exercise delayed the excretion of the second batch of lactic acid even further.

A study by Jones et al. [16] suggested that abnormal lactate responses to exercise and excessive acidosis were consistent with impaired capacity for mitochondrial ATP synthesis [16], and also that “total post-exercise acid exposure is of the order of 50-fold higher in CFS patients exercising to the same degree as normal controls, with no reduction in this pattern of sustained high level acidosis with repeat exercise” [16], and Wong et al. [19] reported that ME/CFS patients reach exhaustion much more rapidly than normal subjects, at which point they also have reduced intracellular concentrations of ATP. And they concluded that their data suggest a defect of oxidative metabolism with a resultant acceleration of glycolysis in skeletal muscles of CFS patients [19]. And the findings by Jones et al. and Wong et al. are confirmed by this study.

The abnormally high lactate production after exercise, also found by other studies [16, 43, 44], the lactate excretion which is split in two and severely delayed, in combination with my symptoms are consistent with an impaired oxidative phosphorylation whereby the anaerobic energy production, the glycolysis, is helping out to produce energy, which is needed for muscle power, for very simple and trivial activities which one should normally be able to do aerobically and not anaerobically. And with each relapse the oxidative phosphorylation becomes more impaired and my muscles have to rely more and more on the anaerobic energy production, which means that how far I can walk becomes less and less, yet at the same time for increasingly more trivial exercise I produce fast amounts of lactate.

A number of other studies have observed that ME patients have reduced cardio-respiratory reserve with a lower anaerobic threshold than sedentary controls [1,13,16]. One implication of a lowered anaerobic threshold would be increased reliance on anaerobic as opposed to aerobic metabolism with increased lactic acid production within the muscles as a result of over-utilisation of the glycolysis.

Some less familiar with this disease could think that this low exercise capacity is due to deconditioning. However, a phenomenon which is not observed in sedentary controls and seems to be unique to ME (CFS) is the profound negative effect of a Cardio Pulmonary Exercise Test (CPET)

on the performance indicators, like VO₂ max, 24 hours later at a second CPET [1,13].

Furthermore, a number of studies showed that deconditioning is not the reason for the exercise intolerance in ME/CFS. For example Vermeulen et al. found that “The high increase of the cardiac output relative to the increase of oxygen uptake argues against deconditioning as a cause for physical impairment in these patients.” [45]. Snell et al. demonstrated and concluded that a second exercise test might be necessary to document the atypical recovery response and PEM, which can be severely debilitating and distinguishes ME/CFS patients from sedentary controls [46].

Jones et al. [16] reported that “total post-exercise acid exposure is of the order of 50-fold higher in CFS patients exercising to the same degree as normal controls, with no reduction in this pattern of sustained high level acidosis with repeat exercise” [16], which means that exercise therapy is not the answer because there is an underlying metabolic problem, and “this sustained acid exposure contribute significantly to the expression of fatigue in CFS” [16]. And Shafran noted “There is no consistent evidence for myopathy or physical deconditioning” [47].

Paul et al. objectified the delayed muscle recovery from fatiguing exercise in ME/CFS [12], Black et al. found that people with ME/CFS, contrary to sedentary controls are unable to reach exercise targets because of exercise intolerance and that GET causes “pronounced worsening of symptomology” which means that “subjects with CFS had reached their activity limit” [31] and Bazelmans et al. concluded that “Physical deconditioning does not seem a perpetuating factor in CFS” [48].

And a review by Twisk showed that a number of studies using two day CPET implicate that the aerobic oxidative phosphorylation fails to respond adequately to exercising in ME/CFS [49].

Furthermore, I had the abnormal delayed muscle recovery after doing trivial things from the very first day of this disease as mentioned before and without all the relapses, I would still be able to walk 20 to 30 yards and my legs would still need 15 minutes to recover from this. Just as they did on the very first day of this disease.

My very high lactate levels after this trivial walk also show that this trivial walk is very strenuous exercise for me which I have been doing twice a day for a number of years and if exercise would really be the answer to this disease, on the one hand I would not have fallen ill with this disease and on the other I would have long exercised myself back to full fitness as my very high lactate levels show that I do my utmost.

The current study is the first one I’m aware of, to look at the bioenergetic problems in severe ME, in which the bioenergetic problems are not only much more pronounced than in mild or moderate ME but are also the reason why many people with severe ME are bedridden because they do not have enough muscle power to sit, stand or walk anymore.

As noted before the main characteristic of ME is an abnormally delayed muscle recovery after doing trivial things [11]. The more the aerobic energy production becomes impaired the more trivial the things that you can do become. And at the same time the lactic acid excretion from the muscle cells becomes more impeded and split into two, which is responsible for the delayed muscle recovery. And the combination of these two, i.e. the impaired aerobic energy production and the impaired lactic acid excretion, cause the main characteristic of ME, the abnormally delayed muscle recovery after doing trivial things [11].

Intracellular immune dysfunctions restrict exercise capacity in ME and vigorous exercise further worsens this [50]. Repeated strenuous exercise in healthy people is characterized by concomitant impairment of the cellular immune system and increased inflammation [51,52].

And even though in my case we're only talking about walking to the toilet and back, judging by my symptoms combined with my lactate levels, this trivial walk constitutes very strenuous exercise for me. ME patients have a more pronounced response in the complement system (i.e. C4a split product levels) [50], lengthened and accentuated oxidative stress [44,53-57] illustrated by abnormal levels of the three markers of oxidative stress (thiobarbituric acid-reactive substances, TBARS, reduced glutathione, GSH, and ascorbic acid, RAA) after exercise as found by Jammes et al. [57] and an alteration in the immune cells' gene expression profile after exercise [50] which correlate with the muscle fatigue and muscle pain, two of the major problems in ME/CFS, whereas no gene expression changes occurred following exercise in healthy controls [58,59].

Hornig et al. [60] found that early ME/CFS cases, disease duration of less than 3 years, had a prominent activation of both pro- and anti-inflammatory cytokines as well as dissociation of intercytokine regulatory networks. And Hornig et al. also [61] found a markedly disturbed immune signature in the cerebrospinal fluid, consistent with immune activation in the central nervous system, and a shift toward an allergic or T helper type-2 pattern associated with autoimmunity. The same changes to the immune system were reported in the blood of people with ME/CFS with long-standing disease. Many of these immune changes relate to post-exertional malaise in CFS, a major characteristic of the illness [50] and play an important part in further increasing the delayed recovery time after trivial, yet for ME patients very strenuous exercise.

In a dose-dependent manner, intramuscular infusion of combinations of protons, lactate and ATP, metabolites normally produced by exercise, act in combination to activate sensory neurons in the dorsal root ganglions (DRG) which produced significant sensations of (muscle) fatigue and muscle pain [62,63].

And dorsal root ganglionitis was found in the autopsies of Sofia Mirza and Lynn Gilderdale [2], two patients who died (in) directly of (very) severe ME.

The muscles in many people with (very) severe ME are very sensitive to even the slightest touch, and in combination with the autopsy findings [2] it is suggestive that dorsal root ganglionitis is responsible for this and chronically inflamed dorsal root ganglions are obviously much more sensitive to exercise metabolites, than healthy non inflamed DRG. And it's likely that these metabolites, which are produced in high quantities by trivial exercise in this disease, as shown by this and other studies [16,43,44], also contribute to the muscle fatigue and muscle pain and the abnormally delayed muscle recovery time in ME/CFS.

In the brain one can have a similar problem as in the muscles i.e. an abnormally delayed brain recovery after doing trivial things. Mathew et al. [64] found that the mean ventricular cerebrospinal fluid lactate concentrations measured by (1)H MRSI in CFS was increased 3.5 fold when compared to healthy volunteers. And a review by Morris et al. [65] found similar findings in a number of other studies.

Patients complain of abnormally long brain recovery times, often called brain fog, which is very well illustrated by the following example. A few years ago when I could still make a telephone call, lasting 5 minutes, my brain needed a whole day before I could make a similar phone call lasting 5 minutes again. As it is the same problem of abnormally high lactate levels combined with abnormally long recovery times, in the same disease, it's very likely that the combination of an impaired aerobic energy production and an impaired lactic acid excretion are responsible for this just like they are in the muscles. And the same applies to the further lengthening of the recovery time by the immune products, including intracellular immune dysfunctions, and by lengthened and accentuated oxidative stress, as found by other studies, but also by exercise metabolites, in a similar way

as they contribute to the abnormally delayed muscle recovery.

When I was a medical student, one of the professors taught us that during the 1930s an exercise experiment whereby participants had to eat a copious meal and directly after had to do strenuous exercise on an exercise bike had to be cancelled after a number of the participants died during this experiment. The problem was caused by too much oxygen going to the stomach and not enough to the muscles and heart. Searching PubMed etc however I wasn't able to find an article about this experiment, which is probably due to the fact that it was done in the 1930s, so long before the advent of the computer and PubMed.

When my meal was only one hour before the exercise, the amount of oxygen going to my muscles was a lot less than when my meal was 2 - 2 1/2 hours before the exercise. That difference had a very negative effect on my aerobic energy production, my lactic acid excretion and my muscle power and pain.

Could the problem be related to a problem with the glucose uptake as the energy production not only requires oxygen but also glucose which just like oxygen must enter the cell. However if there would be a problem with the glucose uptake by the muscle cells or their mitochondria, then both the aerobic energy production and the anaerobic glycolysis would be impeded, because both pathways need glucose. The consequence of that would be that the anaerobic energy production would not be able to assist, and therefore I would be producing almost no lactate instead of producing a lot of it. A lack of oxygen however affects the aerobic energy production but not the anaerobic glycolysis and that leads to the production of large amounts of lactate just to be able to do a trivial exercise and that's exactly what happens when I walk the trivial distance to the toilet and back.

The unexpected finding that the lactic acid excretion from the muscles is impeded a lot more if I eat less than 3 hours before walking the trivial distance to the toilet and back, which for me is very strenuous exercise, shows that when the oxygen is directed to the stomach away from the muscles to help digest the food, even less oxygen becomes available to the muscles and the aerobic energy production becomes even more impeded and the split excretion of lactic acid becomes split even further.

Vermeulen et al. found in 2010 [66] that the decrease in mitochondrial ATP synthesis in ME patients is not caused by a defect in the enzymes of the oxidative phosphorylation but that there must be another defect in the energy production responsible for the exercise intolerance in this disease. And in 2014, Vermeulen et al. [45] found low oxygen uptake by muscle cells which causes exercise intolerance in a majority of ME patients, despite a high increase in the cardiac output. Which means that there is a problem with the oxygen uptake by the muscle cells or their mitochondria, confirming my finding.

If you combine that with the Norwegian Rituximab trials [7, 67] which are suggestive that ME is an autoimmune disease and the findings from Hornig et al. [61] that the immune abnormalities they found are associated with autoimmunity, than that suggests that antibodies are directly or indirectly blocking the oxygen uptake into the muscle cells or their mitochondria.

The Norwegian Rituximab studies not only suggest that ME is an autoimmune disease but also show that two thirds of responders are still in remission at the 36-month follow-up [7]. This clearly suggests that the underlying problems in ME are reversible if patients get the right treatment.

And these findings provide a new way for approaching this disease to find these antibodies and develop a test to detect these antibodies so that that can be used as a diagnostic test, to make it easier for doctors to diagnose this disease and easier to select patients for studies who actually have the disease, contrary to studies that used the Oxford criteria

[68] which were created so that people with other conditions could be included in so called ME/CFS studies, and the American P2P recently concluded that the Oxford criteria confound the ability to interpret the science, that “continuing to use the Oxford definition may impair progress and cause harm. Therefore, for progress to occur, we recommend that this definition be retired” [3], and that more medication trials can be started so that finally effective treatment for this debilitating neuroimmune disease becomes available.

The underlying metabolic problem also makes it clear why exercise therapy or behavioral therapy will not cure or dramatically improve the level of functioning unless medication that deals with the underlying problem becomes available and then exercise therapy or sport will be a good adjuvant. Just like, it is for everybody else in our (western) society.

Falk Hvidberg et al. [69] recently found that patients with ME/CFS have the lowest health-related quality of life of 21 conditions looked at which included patients with chronic renal failure, ischemic heart disease, a number of cancers including lung cancer, strokes etc. The study by Falk Hvidberg et al. [69] confirms the findings from the health status report by Komaroff et al. from 1996 [70]. It also means that nothing has changed in the health situation of ME/CFS patients in the last 20 years and that means that the current 2 available treatments, CBT and GET, which have been heavily promoted for more than 20 years as the treatments for ME/CFS, which most ME patients have tried, because they desperately want to get better, are not effective at all, or even harmful, as patients have been saying for a long time [32] which was confirmed and objectified by Black et al. [31]. And the American Institute of Medicine recently concluded that there are no effective treatments for this serious and debilitating disease [71].

With the above findings of the underlying metabolic problem in this disease, it is easy to understand why these two treatments are not effective. And the alarming findings by Falk Hvidberg et al. [69] further emphasize the urgent need for effective treatments for patients with this debilitating disease.

Conclusions

This study was the first, or one of the first, to look at the underlying bioenergetic problem in severe ME. As found by other studies in patients with mild to moderate ME, this study found that in severe ME, patients have an impaired oxidative phosphorylation [16,43,44,64] but it also found an impaired lactic acid excretion by the muscle cells and the combination of these two is responsible for the main characteristic of ME, i.e. the abnormally delayed muscle recovery after doing trivial things [11]. The muscle recovery is further delayed by many of the immune changes, including intracellular immune dysfunctions, as found by other studies [50], which further restrict exercise capacity in ME, but also by lengthened and accentuated oxidative stress [44,53-57], and by exercise metabolites, which work on the sensitive receptors in the Dorsal Root Ganglions [60,61], which in ME are chronically inflamed, as demonstrated by the dorsal root ganglionitis found in autopsies of a number of patients with severe ME [2], and are therefore much more sensitive to these exercise metabolites, which are produced in (very) high quantities in response to trivial exercise, which for ME patients, due to the underlining metabolic problem, is (very) strenuous exercise.

In the brain one can have a similar problem as in the muscles, i.e. an abnormally delayed brain recovery after doing trivial things. As it is the same problem in the same disease, and a number of studies have found large amounts of lactate produced by the brain [62,63], it's very likely that the combination of an impaired aerobic energy production and an impaired lactic acid excretion are responsible for this and that the brain recovery is further delayed by the immune products, including intracellular immune

dysfunctions, by a lengthened and accentuated oxidative stress, but also by exercise metabolites, in a similar way as in the muscles.

This study also shows that the impaired oxidative phosphorylation and the impaired lactic acid excretion by the muscle cells are caused by an impaired oxygen uptake by the muscle cells or their mitochondria and in combination with the Norwegian Rituximab studies [7, 65], which suggest that ME is an autoimmune disease, it is likely that antibodies are directly or indirectly blocking the oxygen uptake into the muscle cells or their mitochondria. Blocking the entrance of oxygen into the cell, by directly binding to the oxygen itself or indirectly by changing something in the cell membrane effectively. And the more impaired the oxygen uptake gets, the more muscle power the patient loses, the more severe this disease becomes and the more disabled the patient becomes.

Further research with patients with severe ME, so that we know they have the disease and not something else, is needed to find these antibodies, so that a reliable diagnostic test can be developed for patients with this debilitating disease, as highlighted by the alarming findings by Falk Hvidberg et al. [69] that patients with this disease have the lowest quality of life of 21 diseases looked at, which included patients with chronic renal failure, a number of cancers including lung cancer, strokes etc.

The study by Falk Hvidberg et al. [69] confirms the findings from the health status report by Komaroff et al. from 1996 [70]. It also means that nothing has changed in the health situation of ME/CFS patients in the last 20 years and that means that the current 2 available treatments, CBT and GET, which have been heavily promoted for more than 20 years as the treatments for ME/CFS, which most ME patients have tried, because they desperately want to get better, are not effective at all, or even harmful, as patients have been saying for a long time [32], which was confirmed and objectified by Black et al. [31] and the American Institute of Medicine recently concluded that there are no effective treatments for this serious and debilitating disease [71] and it's long overdue that ME/CFS patients get proper medication so that they get their health and independence back, can come off benefits and go back to work.

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Competing Interests

No competing interests.

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