

Myalgic Encephalomyelitis (ME): A Haemorheological Disorder Manifested as Impaired Capillary Blood Flow

Leslie O. Simpson, Ph.D.¹

Abstract

The differences between the concepts of myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS) are discussed with particular reference to the problems arising from the multiple definitions of fatigue. It is pointed out that our earliest published work with ME patients showed altered blood rheology and subsequent tests using scanning electron microscopy of immediately fixed blood samples provided a basis for understanding the poor blood filterability described earlier.

The consequences of stiffened, shape-changed red cells would be to impair capillary blood flow particularly in tissues with smaller than usual mean capillary diameters. The degree of reduction in the rates of delivery of oxygen and nutrient substrates would be related to symptom severity. As there have been a number of previously reported studies of the red cells in a number of chronic disorders, the observation is not new. Furthermore, the changes in red cell shape populations which occur in ME also occur in other chronic disorders so red cell shape analysis alone is not diagnostic for ME. The observed changes are probably of importance in the pathogenesis of tiredness.

Patients benefit from the results of red cell shape analysis test as it provides evidence of a change which can explain their illness, even if they are unresponsive to treatment. As changes in rheology can be shown to occur in the blood of ME patients, haemorheologic agents which have the potential to improve the flowproperties of blood are recommended as therapeutic agents.

1. Department of General Practice, P.O. Box 913 Dunedin, New Zealand

Introduction

This paper provides an opportunity to publish the introductory lecture on myalgic encephalomyelitis (ME) which I have presented to members of ME organizations in five countries during the past seven years. At the outset it seems necessary to explain the basis for my preference for ME rather than chronic fatigue syndrome (CFS) used either as a synonym or an alternative to ME. While recognizing the etymological inaccuracy of ME, it is a fact that ME organizations had been in existence for many years before a committee of 18 Americans introduced the term CFS and put forward their research criteria for the syndrome.¹ Since its introduction, many Americans have objected to the term and there are reports that one of the original committee now considers CFS to be a terrible name because it trivializes the illness. More importantly, from the patients' point of view, is the claimed importance of neuropsychiatric symptoms in CFS diagnostic criteria. Recently, an influential English psychiatrist stated that chronic fatigue syndrome and psychiatric disorders go together.² But a potentially greater problem associated with the general use of CFS lies in the difficulties arising from the multiple definitions of "fatigue." As early as 1921³ it was recommended that the term fatigue be absolutely banished from precise scientific discussion. Now the term is defined differently in different disciplines and there is an obvious lack of precision. Kennedy⁴ noted that, "The status of fatigue as a physiological response, psychological perception or a symptom of physical or psychiatric disease remains unclear." Even earlier Sir John Ellis⁵ had pointed out

that although malaise and fatigue are terms which recur throughout medical textbooks patients hardly ever use these terms. This implies that an entry in a patient's notes, "suffers from fatigue," indicates the doctor's belief that the different terms used by patients all mean the same thing, which may or may not be true. A dictionary definition of fatigue is "to exhaust the strength by severe or long-continued exertion," but I have yet to meet the ME patient who needs long-continued exertion to initiate their pervasive weariness. For that reason alone "fatigue" is not relevant to the tiredness of those with ME. Given the enthusiasm for CFS of various committees, it seems that there is an urgent need to publicize a definition of fatigue which will overcome the problems which Muscio³ found insoluble in 1921. But even if that problem is solved there seems to be a lack of logic in replacing an imprecise (but generally accepted) term with an even more imprecise term.

The Background to the Present Concept

Early in 1984, members of the Dunedin ME Support Group were interviewed to ascertain the nature of their symptoms and the impact on their work capacity and on their family life. The strongest lasting impression was the total lack of uniformity of symptom patterns. These were so diverse that no pattern of potential associations was discernible. At the Support Group's 1984 annual general meeting, members were informed of the lack of an identifiable pattern which might have provided some clues of causality, but it was possible that for some unknown reason there was a generalized impairment of blood flow. Subsequently this possibility was explored by assessing the filterability of fresh EDTA-anticoagulated blood samples from blood donors and members of the ME support group. The results showed that the filterability of ME blood was significantly poorer than that of blood donors.⁶ In retrospect, this demonstration of changed blood rheology, manifested as a reduced ability to filter through 5/ μ m pores, appears to be the

first report of pathology in ME. According to their text, those results simulated a study of the shape of red cells from ME patients by Mukherjee et al⁷ but as they did not study immediately fixed blood cells it is highly probable they were observing preparation artefacts. Miller et al⁸ had reported in 1976 that they were unable to prevent unfixed red cells from changing shape. Yasuda et al⁹ confirmed that observation and noted that procedures before fixation greatly affect the shape of erythrocytes.

As multiple sclerosis (MS) patients also suffer from tiredness and easy exhaustability on exertion, MS blood was studied and found to be poorly filterable also.¹⁰ Because there was no basis for explaining why ME and MS blood should share the common feature of being poorly filterable it was decided to use scanning electron microscopy (SEM) to ascertain if there was some visible explanation for the increased stiffness of the red blood cells. A simple, easily reproducible technique was devised by adapting the system used for rapid electron microscopy of theatre specimens. This involved immediate fixation in a 2.5% solution of glutaraldehyde in 0.1 M cacodylate buffer at pH 7.4. After overnight fixation at room temperature, samples were dehydrated in ascending concentrations of ethanol to absolute then transferred to pure dry acetone. A drop of the acetone suspension was placed on a cover glass fixed to an aluminum pinstub with double-sided adhesive tape, air dried, gold coated and photographed at 1300X in a Stereoscan 360X microscope using a working distance of 20 mm at 10 Kv.

While the results were found to be reproducible they were not what were expected. Textbooks claim that at rest all red cells are biconcave discocytes but SEM of immediately fixed red cells from healthy blood donors revealed that the cells could be classified into six different shape classes established upon simple, descriptive criteria. Cells could be biconcave discocytes or flat cells or cells with surface changes or cup, basin or dish shaped (early cup

forms) or swollen and dimpled (late cup forms) or have altered and irregular margins.¹¹ A literature search revealed that Kayden and Bessis¹² had noted in 1970 that although red cells are supposed to resemble doughnuts or life preservers, not all cells in any field show such forms. Studies of immediately fixed red cells from healthy Japanese¹³ and healthy Russian subjects¹⁴ showed similar diversity of red cell shapes. It is significant that no reference to these studies has been located in medical text books. In addition there are reports of studies of immediately fixed blood samples from patients with Muscular Dystrophy,⁸ Huntington's disease,¹⁵ and spinocerebellar degeneration,⁹ so neither the technique nor the observations are new. The novel aspect is the classification based upon simple, descriptive criteria.

A strange finding in this general field is that an authoritative, two volume, reference work, *An atlas of blood cells*,¹⁶ should publish two illustrations featuring red cells and ignore the content of the illustrations. Their Fig.12a shows 33 stained red cells and the caption draws attention to a normal erythrocyte which is arrowed and shows a clear centre "due to the biconcavity of the cell." But only one of the 33 cells shows this feature and there was no comment about the 32 cells which lacked clear centres. Their Fig.12b is a scanning electron micrograph of 39 red cells over the caption, "erythrocytes appear as biconcave discs by scanning electron microscopy," but only six or seven cells have that form. There are clearly discernible flat cells, cells with ridges and dimpled cells, all of which were simply disregarded. It is surprising that these illustrations have not stimulated critical comment from haematologists who would be the main users of such books.

The results from red cell shape analysis of ME blood samples

Up until 1989 all blood samples from ME patients had increased percentages of cup transformed cells (stomatocytes),¹⁷

which are considered as the marker for "acute" ME. However as increased cup forms may persist for some years it is not acute in the usual medical sense. Data presented at the Cambridge Symposium on ME in 1990 also showed that increased cup forms was the most common change, but it also showed that a small number of both sexes had increased percentages of cells with altered margins.¹⁸ Increased percentages of those cells, or of flat cells or cells with surface changes are markers for "chronic" ME.

In the Cambridge Symposium report it was noted that 50% of cases with "acute" ME responded to an injection of 1 mg of vitamin B₁₂ as hydroxocobalamin, with the loss of their symptoms within 24 hours. However, symptoms will return and when they become severe they should request another B₁₂ injection. There are cases who have lived virtually normal lifestyles while having B₁₂ injections at 12 to 20 day intervals. In one such case it was found that the B₁₂ injection gave no relief and the assessment of a blood sample revealed that the increased cup forms had been replaced by increased cells with altered margins, indicating a shift from acute to chronic ME. Paired blood samples labelled pre and post B₁₂ received from general practitioners showed that 48% contained fewer cup forms after B₁₂ and 52% had more or were unchanged. So those independent data are supportive of the observation that only 50% of cases with increased cup forms respond to B₁₂. The reason for this is not known.

Some insight into the mechanism involved can be gained from two sources. Ellis and Nasser¹⁹ reported a placebo-controlled study of the effects of B₁₂ in the treatment of tiredness. They injected 5 mg of B₁₂ as hydroxocobalamin twice weekly for two successive weeks. All subjects experienced a sustained relief from tiredness and as blood levels of B₁₂ were measured it was emphasized that the participants did not suffer from B₁₂ deficiency, i.e. perni-

cious anaemia. Unexpectedly there arrived a blood sample from a case of untreated pernicious anaemia which contained a similar percentage of cup forms to cases with ME. As has already been noted, 50% of cases of ME with increased cup forms reported a loss of symptoms after an injection of B₁₂ which was associated with a reduction in cup forms. A text book of haematology notes that within 24 hours of an injection of vitamin B₁₂, patients with pernicious anaemia experience a surge of well being. As their anaemic status does not improve for three or four days, it is possible that the improvement in well being is the result of improved capillary blood flow subsequent to a transformation of cup forms. However those observations fail to explain why only 50% of ME cases respond.

While some doctors express concern about possible toxic effects resulting from multiple injections of vitamin B₁₂, a recent review expressed the opinion that there was neither benefit nor toxicity associated with high dose levels of the vitamin.⁴¹

Between July 1, 1992 and the end of 1995, 897 blood samples were received from ME patients in New Zealand. More than 70% of such samples came from general practitioners. An analysis of the results of the red cell shape revealed that less than 5% of cases had increased cup forms typical of "acute" ME with a vast majority of cases having "chronic" ME with increased percentages of flat cells. About 12% of cases had cells with altered margins and 7% had increased cells with surface changes. So the results indicate that between 1990 and 1992 there was a shift from "acute" to "chronic" ME and the basis of the shift is unknown. It should be emphasized that there appears to be no difference in the nature or severity of symptoms in the "acute" or "chronic" phases, but the treatment is different (see below). In addition it should be noted that there is a good correlation between how people feel at the time of blood sampling and the results from the sample. Samples drawn

from subjects who are well at that time will usually show no abnormality of red cell shape but samples drawn when a patient is unwell or has been exposed to a stressful situation will have shape-changed red cells.

The Results from Red Cell Shape Analysis in other Chronic Disorders

Although tiredness and easy exhaustability on exertion are major symptoms of ME such symptoms are common in other chronic disorders. The results from red cell shape analysis of blood samples from patients with MS,²² AIDS,²⁴ and Occupational Overuse Syndrome²⁶ have been published and there are unpublished results relating to both type 1 and type 2 diabetes, systemic lupus erythematosus, leprosy and post-polio syndrome. In all disorders there were changes in the cell shape populations.

As the effects of changes in the shape populations of red cells will be to impair capillary blood flow, it is not surprising that in conditions shown to have changes in red cell shape populations there is evidence of reduced cerebral blood flow as demonstrated by xenon washout or by single photon emission computed tomography (SPECT). Therefore, because changes in red cell shape populations occur in other chronic disorders, red cell shape analysis cannot be diagnostic of ME. But it should be recognized that the analysis demonstrates the presence of changed red cell populations in blood which is considered to be normal on the basis of automated blood screens. Therefore red cell shape analysis identifies changes which are probably important in the pathogenesis of tiredness. As early as 1960 it was considered that inadequate availability of oxygen was the first cause of tissue cell exhaustions which led on to clinical tiredness.²⁸ Normal tissue function is absolutely reliant on the capillaries of the microcirculation to deliver their metabolic needs. Events which by impairing capillary blood flow result in inadequate rates of delivery of oxygen and

nutrient substrates will have the greatest adverse effect on those tissues with great metabolic activity and a high demand for substrates, such as muscles and secreting glands. Nervous tissue is particularly sensitive to oxygen deprivation and Tower²⁶ has pointed out that the brain has no capacity to store oxygen and can store a minuscule amount of glucose. Thus normal brain function is absolutely dependent upon the maintenance of normal rates of capillary blood flow to deliver those essential metabolites. Such observations imply that when reduced cerebral blood flow can be demonstrated brain function must be impaired commensurately. While it is claimed that psychological, psychiatric and cognitive problems are primary features of ME it seems more likely that such morbidity is more likely to be a consequence of impaired cerebral blood flow. As early as 1967²⁷ it was stated that impaired blood flow in the hypothalamus gave rise to similar cerebral symptoms to those reported by ME patients. Evidently psychiatrists have realized that it would be difficult to substantiate a claim for a primary role of psychiatric disorder in fatigue states if it could be shown that impaired cerebral blood flow was part of the disorder. This could explain why psychiatrists should challenge the validity of claims of altered cerebral blood flow by means of neuroimaging techniques²⁸ but given the ubiquitous effects of shape changed red cells it would be surprising if normal brain blood flow persisted. For the above reason, psychologists/psychiatrists may be faced with the challenge of separating the manifestations of brain dysfunction due to inadequate rates of delivery of essential metabolites from the usual causes of psychological/psychiatric morbidity and pathology.

The Benefits of the Results of Red Cell Shape Analysis for ME Sufferers

Perhaps the most disabling aspect of ME is the unknown aspect of the disorder as both medical examinations and labora-

tory tests reveal no abnormalities. In New Zealand, at least, it seems that despite being assured by their doctor that there is nothing wrong with them, patients continue to feel unwell and worry that they have a psychologic or psychiatric disorder. Worry and other stressful events have adverse effects on red cell shape and are likely to enhance symptom severity. The results from red cell shape analysis are set out on a table showing the percentages of the different red cell shapes together with an electron micrograph and an explanation sheet. When patients see the evidence of changes which can explain why they feel unwell they cease to worry and normal capillary blood flow results and symptoms disappear.

The most common causes of relapses in New Zealand are episodes of anxiety or emotional stress or over exertion. In these circumstances the adverse consequences are probably mediated by the effects of catecholamines on red cell shape. The probable mechanisms involved have been described²⁹ together with the postulate that those who suffer from ME have an anatomical basis for their disorder, i.e. that they have mean capillary diameters which would fall in the first quartile of a size distribution of mean capillary diameters. This concept provides a basis for understanding why only one member of a family goes on to develop ME even though all members of the family had suffered from the same viral infection.

The concept also helps to understand the diversity of presenting symptoms. Regions evincing symptoms would be considered to have smaller than usual capillaries. The overall implications of the concept are that subjects with smaller than usual capillaries would always be at risk of becoming symptomatic when there was a shift in the shape populations of red cells. For that reason those with ME are given three pieces of advice which aim to prevent changes in red cell shape.

Rule 1. If you see an argument developing, break off and do not put your health

at risk be becoming involved.

Rule 2. If you sense a stressful event developing, vote with your feet and leave the vicinity.

Rule 3. Find out what is the upper limit of physical activity that you can get involved in without suffering a relapse. When you have established your limit then you should begin to increase your capacity by regular, gentle activity. For example, commence by walking to the nearest power pole and back, every day for a week; walk two power poles next week, then three power poles and so on so that your exercise is gentle and your increments slight.

Treatment Options to Consider

As the primary observation of poorly filterable blood has been reinforced by the finding of shape changed red blood cells, it seems clear that altered blood rheology is an important factor in ME. For that reason treatments should be based upon agents which improve the flow properties of blood, i.e. haemorheologic agents. As already mentioned, vitamin B₁₂ had the effect, in 50% of cases, of reducing the number of cup forms in the blood. It seems that because such cells are so poorly deformable they have an adverse influence on capillary blood flow even at relatively low percentages.

For the 90–95% of cases with “chronic” ME, the most successful treatment so far is dietary supplementation with evening primrose oil. However it is possible that many oils bearing such a label may be spurious. In 1980 the New Zealand Institute of Chemistry reported on the make-up of materials sold as evening primrose oil. Of 11 brands, only two were evening primrose oil. It is possible that the majority of evening primrose oils are true to label, but a drug store in Fredericton, New Brunswick displayed an evening primrose oil with 15% gammalinolenic acid (GLA), which meant that it was not evening primrose oil as it contains between 9.1 and 9.3% GLA.

Therefore, at this time, only the three brands for which independent verification of the makers' analysis have been seen are recommended: Efamol, Naudicelle and EPO.

Evening primrose oil contains two omega-6 fatty acids, cis-linoleic acid and gammalinolenic acid. These are “essential” fatty acids which cannot be made in the body and must be obtained in the diet. Cis-linoleic acid is the most common fatty acid obtained from fresh green vegetables and it is the starting point for the synthesis of the hormone, prostaglandin E₁ (PGE₁). In the normal human body this synthesis is accomplished through the action of a series of enzymes. As far as ME and some other disorders are concerned, the first enzyme which transforms cis-linoleic acid to gammalinolenic acid is the most important because in a number of circumstances the enzyme becomes inefficient and may become inoperative. The enzyme, delta-6-desaturase is adversely influenced by viral infections, by radiotherapy, by diabetes and with increasing age and in each category there is evidence of altered blood rheology. When the enzyme is dysfunctional, gammalinolenic acid formation may be reduced or may not occur resulting in suboptimal levels of PGE₁. It has been shown that PGE₁ increased the fluidity of the lipid bilayer of the red cell membrane and it was considered that this would increase red cell flexibility.³⁰ That observation was confirmed in the following year when it was reported that PGE₁ increased red cell filterability.³¹ Manku et al³² reported that 4 x 500mg capsules of evening primrose oil (Efamol) had no effect on the blood levels of PGE₁ while 8 x 500mg capsules caused a significant increase in PGE₁ concentrations in the blood. The results of that study are the basis for a recommended daily dose of 8 x 500 mg capsules of evening primrose oil, regardless of age or gender. However the oil appears to be effective in only about 70% of cases. If cerebral problems such as

memory lapse, confusional states and brain fog are common symptoms it is suggested that ginkgo extract in the white tableted form be taken at the maker's recommended dose together with the primrose oil for at least six weeks. The ginkgo extract is a bioflavonoid with an impressive literature documenting its beneficial effects on blood flow. If after six weeks there are no discernible benefits then that treatment should be discontinued and the potential of omega-3 rich fish oil should be investigated. It has been shown that omega-3 rich oil improved red cell flexibility but by a different mechanism to that of omega-6 oils such as evening primrose oil. There is good reason to believe that there are many other agents which will be shown to improve blood rheology. There are pharmaceuticals such as Trental, Cinnarizine, Hydergine and Cyclandelate which have this potential. At this time the greatest gap in our knowledge is information concerning the mechanisms which cause red cells to change shape rapidly and dramatically. If that information was available it might be possible to devise a therapeutic regimen which would prevent red cells from changing shape.

Conclusion

The main message in this paper is that you will feel only as well as your capillaries deliver oxygen and nutrient substrates to your tissues. Therefore, when altered blood rheology impairs capillary blood flow there will be an adverse effect on well being. It is not possible to assess or to estimate the range of health problems or their severity which might arise through inadequate rates of delivery of metabolic needs to the tissues in general. But if the metabolic needs of secreting glands such as the pituitary, hypothalamus, thyroid and adrenals are not met, then the consequences could be serious.

Given that the symptoms of adrenal gland dysfunction are not greatly different from those ascribed to neurally medi-

ated hypotension, a surprising feature of a much publicized study³³ was that the investigators did not mention that they had excluded a diagnosis of early Addison's Disease. However one of the drugs mentioned in the study (Florinef) is used in the treatment of Addison's Disease. Crucial to the value of any investigation is the need to ensure that the subjects being investigated do not suffer from some other disorder.

Because the symptoms of ME may wax and wane and may almost disappear for several consecutive days, it is difficult to see how this symptom pattern relates to persisting agents such as organochlorines, urinary markers, bacterial infections or specific enzyme changes. Given the prevalence of studies involving small numbers of CFS patients it seems important to consider what Lock³⁴ considered "the scientific community's false values: the pressures of newness at all costs; the dislike of negative results; and the publish-or-perish syndrome whereby excellence is equated with quantity, leading to inadequate peer review because of the pressures on the referee."

My interest in ME is based solely upon a desire to help a section of the community who suffer from a debilitating illness which has yet to gain general acceptance from the medical community. At the risk of being considered irrational about the biological importance of normal capillary blood flow, I can point with satisfaction to the many ME patients who have benefitted from treatment with haemorheologic agents.

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