On the pathophysiology of ME/CFS

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Introduction

The lack of an accepted pathology for ME/CFS is probably the greatest obstacle to the development of a logical treatment strategy. Any proposed pathophysiology must be able to account satisfactorily for all of the salient features of the disorder. Such features include the body-wide dysfunction which may involve some or all of the major systems – brain and nerves, muscles and secreting glands. Of particular importance is the need to account for the variability of presenting symptoms and their relapsing/remitting nature. It is necessary to explain why healthy-looking subjects, usually with normal laboratory tests, can report problems of memory and mental confusion, tiredness and exercise intolerance with evidence of endocrine gland dysfunction. Such subjects will report also that emotional upsets, stressful events or overenergetic activity results in severe symptom exacerbation which may persist for some days.

Despite a very extensive literature (more than 2 000 publications about various aspects of CFS in the USA since 1988) which documents studies in the fields of biochemistry, immunology and psychology/psychiatry, the lot of the ME/CFS patient has remained unaltered. Thus the application of sophisticated technology to single aspects of the problem has failed to produce a unifying concept which would provide a logical basis for treatment.

This failure of research endeavours has been highlighted by two events in 2002. In the UK the presentation to Parliament of the Chief Medical Officer's Report recognised ME/CFS as a valid disorder. Further research was recommended in the report, but no answer was forthcoming when, in the House of Lords, the Countess of Mar asked what type of research was envisaged. While this highlights the vacuum concerning ME/CFS research in the UK, of possibly greater significance was the announcement by the United States Public Health Service of a new research initiative concerning 'The pathophysiology and treatment of CFS'. This was the first official recognition of the failure of research to provide a basis for understanding the fundamentals of the disorder.

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The following proposals are based upon red cell shape analyses of blood samples from subjects with a variety of chronic dysfunctional states, labelled variously as ME or CFS or CFIDS or ME/CFS, or CFIDS/ME etc. Such samples were the results of lecture tours to speak to members of Support Groups in New Zealand, Australia, South Africa, England, Wales, Scotland, Ireland, Canada and the USA. Several visits were made to each country.

The history of the hypothesis

The primary observation, published in 1986,[1] was that ME blood filtered poorly in comparison with blood donor blood. This finding of altered blood rheology was repeated in a similar study of another condition in which tiredness was a major symptom (MS) and was published in 1987.[2] Those findings stimulated the thought that scanning electron microscopy might provide evidence of why the blood filtered poorly. A simple technique was devised to study red cell shape in immediately fixed red cells and the results quickly showed that in contrast to textbook concepts that all red cells were biconcave discs, the red cells of healthy humans and animals could be classified into six different shape classes.[3] When the red cells of ME patients were studied it was found that there were changed red cell shape populations which would explain why ME blood filtered poorly.[4] Those early findings were reproduced in a review of more than 2 200 samples from ME patients in four countries.[5] Participants who reported that they were well at the time they had their blood sample taken had normal red cells. This association of normal red cell shape populations with an absence of symptoms was explored in a study of subjects who had had a diagnosis of ME at least two years previously. Blood samples and health reports were obtained at four weekly intervals for 40 weeks. The fluctuating nature of their symptoms was reflected in the number of normal samples. At one extreme, 5/37 women had abnormal results for all 11 samples, while one woman had 6/11 normal samples. The most frequent

situation was to have 2/11 normal samples. Such results demonstrated very well the remitting/relapsing pattern of the disorder.

More than 12 000 immediately fixed blood samples from patients suffering from any one of 10 different chronic disorders with unexplained dysfunction as a common problem have been assessed. The results show that altered blood rheology manifested as altered red cell shape populations is a common factor.

Thus a change in a red cell shape population is not a benign event. The effects of shape-changed, poorly deformable red cells are to reduce the rate of blood flow in capillaries, thus reducing the rate of delivery of oxygen and nutrient substrates to the tissues. If the rate of delivery of the metabolic needs is insufficient to sustain normal tissue function, then tissue dysfunction will result.

The hypothesis

It is postulated that the pathophysiology of chronic disorders, including ME/CFS, can be explained in terms of altered blood rheology manifested as changed shape populations of red blood cells.

(a) As a result of exposure to any one of a wide range of agents, including viruses, bacterial infections, emotional episodes, stressful events, physical activity etc., red cell shape populations change. With the loss of discocytic shape, red cells become poorly deformable.

(b) The dysfunctional state of ME/CFS (and many other chronic disorders) is the consequence of inadequate rates of delivery of oxygen and nutrient substrates to the tissues, due to the adverse influence of shape-changed, poorly-deformable red cells on the rate of capillary blood flow.

(c) In accordance with the Poiseuille formula, the rate of flow through narrow tubes is directly proportional to the fourth power of the tube radius. This means that even small differences in capillary dimensions may have a significant influence on the rate of flow which will be slowest in the smallest capillaries. It should be noted that the effects of poorly deformable red cells will be greatest in small vessels.

(d) Tissues most at risk will be those which normally have a high rate of utilisation of oxygen and nutrient substrates, such as the brain and nerves, muscles and secreting glands. So it can be anticipated that such tissues will be common regions for symptoms.

(e) Those individuals with the anatomical feature of smaller than usual mean capillary diameter, i.e. those in the first quartile of a hypothetical distribution of mean capillary diameters, would be most at risk of developing symptoms after exposure to some agent which changed the shape population of their red cells.

(f) Because it is not possible to alter capillary diameter, it is proposed that treatments should be aimed at improving red cell deformability and thus increasing the rate of flow in capillaries.

Discussion

This discussion will deal with each of the above sections in turn.

(a) As red cells lose the nucleus when they leave the bone marrow they are not living cells and they are incapable of independent existence. In both in vivo and in vitro studies, red cells respond to change in their environment by changing shape. However, in the in vivo situation it seems as though some other persisting change is initiated and this has the effect of altering the shape of many generations of new red cells. In such circumstances patients remain symptomatic for many years,

(b) While the term 'fatigue' has been a topic of much debate, the term 'muscle fatigue' is a recognised physiological condition which is a consequence of inadequate oxygen availability. Because phosphorylation is impaired also during oxygen insufficiency, reduced ATP synthesis can account for easy fatigability and weariness. In 1960, George Ffrench[6] used as an example of hypoxic dysfunction, the consequences of being at a simulated altitude of 25 000 feet. Secreting glands have complex capillary beds which will place gland function at risk when there are changed red cell shape populations.

(c) The significance of the size of capillaries is that it provides a basis for understanding the variation in presenting symptoms. Different proportions of large and small capillaries in muscles can explain why different muscles are related to symptoms in different subjects. In any organ or system where there is a capillary bed which by chance has a predominance of small capillaries – be it in muscle, brain and nerves or secreting glands, it will produce a localised region of dysfunction in the presence of poorly deformable red cells.

(d) It is not an accident that most symptoms are referable to tissues with high rates of utilisation of oxygen and nutrient substrates (such as muscles, brain and secreting glands). The expected effects of shape-changed red cells have been reported in studies in which neuroimaging techniques such as xenon washout and single photon emission computed tomography (SPECT) have shown reduced rates of cerebral blood flow in several disorders. Laser Doppler Flowmetry has shown that in a condition with changed red cells, there is a marked reduction in the rate of passage of erythrocytes through capillaries.

(e) The significance of the concept of 'mean capillary diameter' is that it explains why individuals with similar values for altered red cell shapes do or do not evince symptoms. While the effects on red cell shape of a change in the environment is the same, only those with small

capillaries will develop symptoms. As over-exertion changes red cell shape in an additive fashion, there will be an accompanying exacerbation of symptoms. It is worth noting that in a CFS patient with SPECT-demonstrated reduced cerebral blood flow in a pre-exercise sample, the cerebral blood flow was further reduced in a post-exercise SPECT scan.

(f) On the basis of the reports from spin-labelling studies, it seems that increased viscosity of the lipid bilayer of the red cell membrane plays an important role in reduced red cell deformability. Results from other studies imply that this is the outcome of a dysfunctional enzyme (delta-6-desaturase) which catalyses the first stage of elongation of both omega-6 and omega-3 fatty acids. This could lead to a deficiency of prostaglandins E1 and E3. A 1974 study showed that prostaglandin E1 improved the fluidity of the lipid bilayer of the red cell membrane.[7] Kamada et al[8] showed that sardine oil as a dietary supplement increased the fluidity of the lipid bilayer of diabetic red cells to the extent that they could not be separated from non-diabetic cells by spin labelling. In a study which paralleled the effects of sardine oil, it was shown that a daily supplement of 4 000mg daily of evening primrose oil (which provided the gamma-linolenic acid which could not be synthesised when delta-6-desaturase was dysfunctional) resulted in a significant increase in the blood levels of prostaglandin E1. The resulting improvement in red cell deformability led to an increase in the rate of capillary blood flow. However, it is known that neither evening primrose oil nor fish oil improve red cell deformability in all cases and the reason for this is not known. Other agents have the potential to be helpful, and this is an area needing investigation.

References

1. Simpson LO, Shand BI, Olds RJ. Blood rheology and myalgic encephalomyelitis: a pilot study. Pathology 1986; 18:190–192.
2. Simpson LO, Shand BI, Olds RJ, Larking PW, Arnott MJ. Red cell and haemorheological changes in multiple sclerosis. Pathology 1987; 19:51–55.
3. Simpson LO. Blood from healthy animals and humans contains nondiscocytic erythrocytes. Br J Haematol 1989; 73:561–564.
4. Simpson LO. Nondiscocytic erythrocytes in myalgic encephalomyelitis. NZ Med J 1989; 102:126–127.
5. Simpson LO, Herbison GP. The results from red cell shape analysis of blood samples from members of myalgic encephalomyelitis organisations in four countries. J Orthomol Med 1997; 12; 221–226.
6. Ffrench G. The clinical significance of tiredness. Canad Med Assn J 1960; 82:665–671.
7. Kury PG, Ramwell PW, McConnell HM. The effect of prostaglandin E1 and E2 on the human erythrocyte as monitored by spin labels. Biochim Biophys Res Commun 1974; 56:478–483.
8. Kamada T, Yamashita T, Baba Y, Kai M, Setoyama S, Chuman Y, Otsuji S. Dietary sardine oil increases erythrocyte fluidity in diabetic patients. Diabetes 1986; 35:604–611.