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Could Protein Malnutrition of Rapid Onset Explain the Atypical Symptoms of COVID-19 and Consequential Malfunctioning of The Body? A Hypothesis

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Abstract

Many of the wide-ranging symptoms of COVID-19 have not been associated previously with a respiratory illness. A similarity between these atypical symptoms and the symptoms of malnutrition was observed. To investigate, a comparison of COVID-19 symptomatology with recognised states of malnutrition showed a significant relationship that was further explored in a review of the literature. This hypothesis links the atypical symptoms to the effects of increasing protein malnutrition. The rapid appearance of malnutrition symptoms at the beginning of the COVID-19 infection is concurrent with the rapid cell proliferation of the immune system. Although previous work has, in general, assumed that the body is capable of providing for the needs of the immune system during infection, heightened immune activity from the commencement of COVID-19 could require an early increase in energy yielding sources. Should insufficient availability of protein resources occur, this could quickly lead to malnutrition. Any continuing insufficiency, during the active phase of the virus, might result in widespread depletions in the tissues and the consequential malfunctioning of many organs. A new appraisal of the immune system requirements needed to counteract the impact of the novel virus, COVID-19, could show the potential benefit for earlier protein intervention in the disease process. This hypothesis could also have relevance for other life situations where a rapid cell proliferation might occur.

Keywords: Malnutrition, COVID-19, Protein, Immune System, SARS-CoV-2, Cell Proliferation, Starvation

1. Introduction

The novel corona virus, SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2), which causes the disease COVID-19, is understood to have originated in China in 2019. Initially the defining symptoms were reported to be a continuous dry cough, fever and shortness of breath or difficulty in breathing. More data was gathered as the virus spread internationally and to these symptoms were later added a loss or change in the senses of taste and/or smell.

Many other symptoms of COVID-19 have since been reported clinically or anecdotally. These symptoms are wide-ranging and have been seen as puzzling. In this article I will suggest in a new hypothesis that the majority of these atypical symptoms, both physiological and neurological, are similar to those experienced in protein malnutrition. This sudden malnutrition and the consequent catabolism, appearing within days rather than months in COVID-19, could result from insufficient protein availability for the coincident sudden needs of the body when under acute stress. This could adversely affect the proper functioning of many of the body's organs and could also lead onto life-threatening conditions, and the possibility of sepsis.

2. Background to the hypothesis

The immune response to infection sets in motion an early inflammatory reaction and an increase in protein metabolism. When insufficient amino acids are obtained from the diet to supply this increase in protein metabolism, any excess required will be drawn from the skeletal muscles. A continuing insufficiency will eventually result in atrophy of these muscles. The biological mechanisms behind the increased protein metabolism and muscle breakdown during infection are understood, although the response to infection, which appears initially beneficial, can become extremely detrimental to the body [1].

COVID-19 is primarily a respiratory virus, but its spread to so many different non-respiratory organs in the body is unusual. It has also proven a challenge to satisfactorily explain how much of the puzzling and wide-ranging symptomatology is connected to the illness.

A report of a personal experience of COVID-19 in the British Medical Journal, described many varied symptoms, among which were 'weird sensation in the skin with synthetic materials' and 'pins and needles' also 'tinnitus' [2]. Although parethesia and tinnitus can have a variety of causes, being found together was of interest as these odd symptoms were both noted also

in a year-long Semi-Starvation study [3]. Finding that more symptoms similar to those reported in COVID-19 were present amongst volunteers in the same semi-starvation study, led onto an investigation of this coincidence by comparing four instances of malnutrition with that of the novel virus.

This comparison comprised the Semi-Starvation study, which was detailed in The Biology of Human Starvation (Keys et al, 1950) and also the eating disorder of Anorexia Nervosa, which is characterised by extreme dieting and resulting malnutrition [3]. Two further forms of malnutrition were used: Kwashiorkor, a severe form of protein malnutrition and Marasmus, also a severe form of protein-calorie malnutrition. The fifth and final column, for interest, is Ketosis where, in response to low glucose availability during caloric deprivation, increased ketones are produced to provide an alternative and continued energy source for the brain.

Table 1 lists some of the symptoms being reported during the experience of COVID-19. If there were only one or two similarities with these states of malnutrition, this would not be significant, but for so many it was worth considering further what might be happening.

Malnutrition normally takes weeks or even months to develop and produce many of the symptoms shown in Table 1. In Dr. Ancel Keys' Semi Starvation study the young male volunteers were slowly starved over a period of six months and their symptoms recorded during the whole of this time. Anorexia nervosa usually takes months to become apparent. Both Marasmus and Kwashiorkor are slow forms of malnutrition, taking months to develop, and are seen mainly in children in areas where there is an unstable food supply.

	COVID-19	Semi-Starvation study	Anorexia	Marasmus	Kwashior-kor	Ketosis
Fever	✓			✓		
Chilliness	✓	✓	✓	✓		
Fatigue	✓	✓	✓	✓	✓	✓
Lack of energy	✓	✓	✓	✓		✓
Fainting	✓	✓	✓	✓		
Dizziness	✓		✓	✓		✓
Change of taste/ bad taste in mouth	✓		✓			✓
Nausea / loss of appetite	✓		✓	✓	✓	✓
Loss of Muscle Mass	✓	✓	✓	✓	✓	✓
Impaired concentration, alertness, comprehension, impaired cognitive function	✓	✓	✓	✓		✓
Headaches	✓		✓	✓		✓
Gastrointestinal discomfort	✓		✓	✓		✓
Edema /swelling	✓	✓			✓	
Breathlessness (shortness of breath)	✓					✓
Visual disturbances: eye aches, inability to focus, spots in vision	✓	✓	✓			✓
Auditory disturbances: tinnitus, ringing in the ear	✓	✓	✓			
Paresthesias : abnormal tingling & pricking sensations, pins & needles	✓	✓	✓			✓

Diarrhoea/ constipation	✓	✓	✓	✓		
Muscle aches, Joint pains	✓	✓	✓		✓	✓
Dry brittle hair, thinning hair, falls out easily	✓	✓	✓	✓	✓	
Ridged cracked, brittle nails	✓		✓		✓	
Weight loss	✓	✓	✓	✓		✓
Rash varied/ inflamed patches of skin	✓				✓	
Purpura (purple spots patches on skin)	✓			✓		
Menstrual disturbance	✓		✓			✓
Tachycardia, palpitations	✓		✓			✓
Bradycardia, slower heart rate	✓	✓				
Cardiac arrythmia or cardiac arrest	✓		✓	✓		
Dry skin	✓	✓	✓	✓	✓	✓
Dehydration	✓		✓	✓		✓
Weight loss	✓	✓	✓			
Sleep problems	✓		✓			✓
Leucopenia: decrease in white blood cells	✓	✓				

Table 1: Comparison of COVID-19 symptomatology with various states of malnutrition and ketosis

Although in COVID-19 malnutrition has been documented as occurring at a later stage in the illness, when a patient is in the Intensive Care Unit of a hospital, the similarities in Table 1 suggests a different timescale. The indications of malnutrition, normally developing over months, begin to show up in an acute Covid-19 virus infection after only a few days of the illness [4]. If this is happening, it would be a rapid rate of appearance.

What else is happening rapidly at this time? The body's metabolic response to the stress of an infection is complex and diverse and involves massive immune cell activation, as in the activation and propagation of immune cells, the synthesis of an array of molecules requiring DNA replication, RNA expression, protein synthesis and secretion [5].

This significant increase in cell proliferation, includes the positive acute-phase proteins, which at the height of the catabolic response to an infection might rise by a total of 1.2 grams for each kilogram of body weight [6]. Also required are sufficient branched chain amino acids (isoleucine, leucine and valine) to help up-regulate the immune response, act as fuel sources and synthesise protein [7]. T cells will proliferate rapidly and require increased supplies of the essential amino acid methionine as crucial for their activation and continued energy [8].

Although the normal, everyday functioning of the immune system relies on sufficient protein availability from a well-nourished body, with the onset of infection, the heightened activity of the immune system, will require a significant increase in energy yielding sources [9,10]. This additional energy will be expected from the diet in order to mount an effective immune response. Any deficit in the supply of energy will be seen in nitrogen losses as the body begins to break down its own tissues.

The dietary demands would happen suddenly at the very start of infection. These urgent requirements are seen in the nitrogen losses from the beginning of the fever response, which increase and persist for days to weeks after the fever [11].

3. Hypothesis

It is hypothesised that the rapid proliferation of many new cells in response to an episode of acute physiological stress, as well as the activation of cells during infection, induces an increased demand for complete proteins of equally rapid onset. If resources for fulfilling this sudden high protein demand at that time are not readily available, a rapid onset protein malnutrition would ensue as the body quickly begins to catabolise its own tissues. The whole body would be affected adversely.

It is further hypothesised that in the case of the novel virus, COVID-19, the unrelenting protein demand for the rapid and continuing proliferation of new immune cells and the continuing physiological stress of the unrecognised infection, whilst the virus is still active, would necessitate an unrestricted and frequently replenished supply of complete proteins, with a full set of essential amino acids, beyond the normal intake level.

4. Indications and intake during a rapid onset protein malnutrition

Many of the symptoms experienced in COVID-19 may be caused by a state of rapidly increasing protein malnutrition from an immune system desperate for protein. These would be the signs that the body is very quickly under more acute physiological stress, in trying to defeat the novel virus, than has been realised. By the time these indications of malnutrition become noticeable, the immune system is already having problems.

The first appearance of symptoms, 2-14 days after infection and accepted by the patient as the start of the illness, might not all have a direct viral cause [12]. Rather, they could be seen as a warning that the immune system response has run out of supplies and is now desperately seeking resources from its own tissues to keep up the fight. They highlight the possibility that the dietary food selection has already proven inadequate for the sudden and pressing needs of the body, causing protein deficiency to rapidly manifest along with possible impairment of the immune system. The body would need additional help from external sources for the energy needed to regain and maintain homeostasis.

A fast-developing state of malnutrition early in the illness would demonstrate what has been occurring during the incubation period of the virus. Interestingly, this does not appear to happen in every case. For those who test positive for the infection but remain asymptomatic, it is possible that their immune system acquired sufficient nutrients for its own needs to successfully defeat the virus, particularly as it has been shown that those who are asymptomatic can have similar viral loads to symptomatic patients [13].

For those who become symptomatic, the length and severity of the illness may depend upon two factors. Firstly, how well they are able to nutritionally support their immune system, initially by their dietary choices and thereafter possibly by the increased frequency of this specific intake. And separately, or additionally, to what extent their body is able to support the tissue damage inflicted, due to the needs of the immune system, when in a catabolic state.

Dietary requirements needed to reduce and reverse protein deficiency in severe infection should have a high calorie value, derived from both protein and carbohydrates. Increasing the nitrogen, and thus the protein intake, has been shown to be beneficial when calories, primarily derived from carbohydrates, are also consumed. In an average person, it was necessary for the intake to be between 2 and 3 times more than the calories and protein normally required for maintenance of body weight and nitrogen balance in a healthy young individual [11].

5. Consequences of rapid onset protein malnutrition in COVID-19

In its own defence and survival against the virus, the body would continue to break down its own tissues for amino acids, maintaining the functionality of the immune cells for as long as it needs to defeat the virus. It has been shown that the immune system can overcome this novel virus, in more than 95% of cases, despite causing possible depletions in nearly all the tissues to varying degrees and, in some patients, quite severe depletions. However, the internal damage wreaked on the body to achieve this victory might take a considerable time to repair, especially in those cases where the extent of the damage is widespread [3].

This hypothesis of protein malnutrition due to the rapid proliferation of high numbers of cells for the immune response to COVID-19, could precipitate any of the following to occur as the illness progresses towards a critical condition and also begin to explain why they might occur:

- All symptoms of malnutrition shown in Table 1 might manifest for reasons dependent on lower availability of sufficient amino acids from the dietary intake at an early stage in the illness and subsequently obtained from the body's own tissues.

- Ketosis in early critical illness is due to the caloric deprivation of accelerating malnutrition in acute conditions and, for those with or without diabetes, could lead on to the later development of ketoacidosis, as seen in COVID-19 [14]

- Intellective capacity could be affected: "As semi-starvation progressed in the Minnesota Experiment, complaints of inability to concentrate for any period of time and of difficulty in developing thoughts became numerous. By the end of the semi-starvation period a large proportion of the men felt that their judgment had been impaired. They reported further that their general alertness and comprehension had declined. According to our clinical impressions, the intellective capacity was essentially unchanged." *(The Biology of Human Starvation. Vol 2 p859)* [3].

- All muscles are in danger of atrophy during malnutrition and starvation as the body uses the proteins in these tissues [3]. This affects their functionality, and in the most severe of cases, where the musculature of the heart and diaphragm dysfunction, this could lead to heart failure [15].

- Severe malnutrition can cause diaphragm weakness and increase risk of respiratory failure [16].

- All organs might atrophy in starvation, with the brain and nervous tissues thought to suffer less. (*The Biology of Human Starvation. Vol 1 Chapters 8 - 18)* [3]. This might ultimately lead to multi organ dysfunction.

- Atrophy of the organs: "The brain and spinal cord lose very little weight in starvation but the other soft tissue show large losses, the liver and intestines perhaps suffering to the greatest extent. The heart and kidneys tend to lose a little less weight than would be proportional to the body weight loss."
(The Biology of Human Starvation. Vol 1 p190) [3].

● Atrophy of the heart: "Cardiac musculature does not seem to differ from the skeletal musculatures in response to starvation except, perhaps that the relative decrease in mass may be slightly less" *(The Biology of Human Starvation. Vol 1 p186)* [3].

● Atrophy of the liver: "In almost all cases starvation or chronic undernutrition produces a marked loss in weight of the liver, though the high degree of normal variability in this organ makes interpretation of individual data difficult. The relative loss of liver weight seems to exceed that of the body as a whole so that the liver weight is subnormal both in absolute and relative terms."
(The Biology of Human Starvation. Vol 1 p191) [3].

● Changes in blood vessels: "... the most significant effect of starvation on the blood vessels is an early appearance of changes ordinarily seen at more advanced ages." "Embolic phenomena are not infrequent."
(The Biology of Human Starvation. Vol 1 p207) [3]

● Brain: "Cytological evidence of degeneration in the brain are frequently but not always seen in starvation. There is a good deal of evidence that the brain is edematous, and in most cases some degree of hyperemia is apparent. Besides vacuolation, cloudy swelling, chromatolysis and fibrolysis are reported occasionally in severe emaciation." (*The Biology of Human Starvation. Vol 1 p191)* (3)

● Nerves: "As a whole, the peripheral nerves show only small histological changes in starvation unless there is also pellagra or beriberi. The nerve fibers themselves are quite resistant, although slight atrophy of the myelin sheath of medullated fibers has been described. The nerve cells more often show degeneration, including vacuolation and chromatolysis, though these are by no means regular or very pronounced phenomena." *(The Biology of Human Starvation. Vol 1 p191)* [3].

● Reduction and exhaustion of the white blood cells could occur when the nutritional resources of the body are insufficient to create new cells and the organs and tissues are being depleted, thus preceding a deterioration in the condition [17].

● Low counts of white blood cells, leukocytes and lymphocytes, have been recorded during COVID-19 infection. Malnutrition, fasting and starvation also drastically reduce levels. (18)

● Many comorbidities increase the risk of aggravation in COVID-19 [19]. As the inflammation that occurs in these conditions already affects nutritional status, the extra stress on nutritional resources could impair the immune system response, when additional amino acids might be suddenly needed to confront a rapidly replicating novel virus.

● Risk factors for the poor prognosis of operative patients, unintentionally scheduled for surgery during the incubation period of COVID-19, could be re-interpreted with this hypothesis, when acute stresses are superimposed on each other [20].

● Age related muscle loss and reduced protein synthesis could badly disadvantage the elderly when they encounter a rapid onset malnutrition as might be found in the metabolic response to COVID-19.

6. Could Sepsis be a further consequence of a rapid onset protein malnutrition?

Sepsis has been defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [21]. It is associated with ongoing protein catabolism with loss of muscle mass, persistent organ failure, neuromuscular weakness and cognitive decline, and the metabolic response during acute sepsis is heavily reliant on the patient's nutritional resources requiring adequate nutritional intake [22]. Coincidentally multi organ dysfunction has been noted as malnutrition descends towards starvation. Is it possible there could be a link between the progress of sepsis, protein deficiency and a rapid onset malnutrition? Might sepsis only become apparent towards the critical end of an already established continuum of deterioration? I pose the question but do not know the answer.

7. Post viral problems of COVID-19

If the hypothesis of a rapid onset protein malnutrition developing at times of rapid cell proliferation, from the beginning and throughout the viral illness, is found to be correct, the post-viral effects of COVID-19 would be widespread and debilitating in those enduring prolonged infection. Due to the probable depletion of amino acids from all of the body's own tissues during the course of the infection, many would be left in a state of protein deficiency and malnutrition, varying from the mild to the severe. The resources of the malnourished body could be low to exhausted, notably the T cells, from the relentless demands recently placed upon it to defeat a novel virus. In the most severe cases, all of the muscles and internal organs could need sustained repair or regeneration from the continual depletion and atrophy of their tissues [23].

For all those affected, even those not hospitalised, a major challenge would be to appreciate that the body is initially not as physically capable as before the novel COVID-19 infection. It could take time for the body to recover, repair and rebuild its damaged tissues and regain strength.

In the literature, recovery from malnutrition has been slowly achieved over weeks or months, dependent upon the severity of the assault, with a gradually increasing intake of calories, protein, and other nutrients [3]. Estimates suggest that for this intake to satisfy the increased demand for protein, it would need to equate to about 20-30 percent more than the normal requirement, depending on the age of the individual [24]. However, it has also been recognised that the restoration of body protein after critical illness is at least 4-fold slower than the rate of loss [25]. In COVID-19, anecdotal reports are showing that recovery is also a slow and lengthy process for nearly one third of those infected.

8. Recommendation

This hypothesis of a sudden protein malnutrition introduces new thinking on the needs of the immune system and its cells in the battle against the COVID-19 infection. Evaluation and validation are required. If the hypothesis is shown to be of benefit, this could

lead to an appreciation of how an increasing cell proliferation, when there is acute physiological or neurological stress, if the nutritional and protein demands remain unsatisfied, could impact the body detrimentally in COVID-19. This knowledge could help alleviate and reduce the damage caused to the body during the infection and possibly in the post viral phase also. There is also the possibility that this detrimental process might not be confined to COVID-19 and could be occurring in other life situations.

Declaration of Competing Interest

The author declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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