Covid-19: acquired acute porphyria hypothesis

Lianne Abrahams

Ronin Institute
127 Haddon Place
Montclair
New Jersey
07043-2314

Correspondence: lianne.abrahams@protonmail.com

Abstract

Pandemic Covid-19 pneumonia, of SARS-CoV-2 aetiology, presents an existential threat to health care systems globally. Multiple therapeutic and prophylactic agents are currently undergoing clinical trial, including 23 clinical trials of (hydroxy)chloroquine in China. While progress towards a curative agent or vaccine is promising, the principal limiting factor in public health emergency is time, and therefore a pre-existing licensed therapeutic would offer reprieve to health care systems operating at the edge of capacity. In this brief communication, the author argues that Covid-19 has high probability of being more than a disease of pneumonia, and that critical Covid-19 patients may be experiencing a form of acquired acute porphyria. Readily available interventions exist to treat acute porphyria and the position is advanced that urinalysis of critical Covid-19 patients would diagnose this pathology.

Erythrocytes are strongly implicated in the pathophysiology of Covid-19. Wuhan University researchers argue that the role of erythrocytes in the pathophysiology of Covid-19 is under-estimated; the co-efficient of variation of red blood cell distribution width (RDW) is predictive of severity of disease state (Gong 2020). Elevated RDW is correlated with reduced erythrocyte turnover; red blood cells become smaller as they age and the delay in clearance expands the low-volume tail of the volume distribution (Patel 2015). Suppressed erythrocyte turnover may indicate erythropoietic distress and function as a compensatory mechanism to maintain circulating red blood cell levels (Patel 2015). Excess porphyrins in red blood cells can precipitate cell lysis and development of hemolytic anaemia (Sassa 2006). Macaques infected with SARS-CoV-2 also have decreased red blood cell numbers (Munster 2020) and susceptibility to SARS-CoV-2 appears to be determined by blood group; blood group A is most affected whereas blood group O seems to be protected (Yang 2020). This finding is concordant with previous studies showing that susceptibility to the 2003 strain of SARS-CoV was determined by blood group (Guillon 2008). Preliminary evidence suggests that CD147, the determinant of the Ok blood group system, binds the spike protein of SARS-CoV-2 (Wang 2020). Incidentally, CD147 functions as an essential receptor for erythrocyte invasion by *Plasmodium falciparum* (Crosnier 2011). Blockade of CD147 abrogates the normal recirculation of erythrocytes, from the spleen into the general circulation, leading to selective trapping of red blood cells in the spleen as development of a form of anaemia (Coste 2001). Autopsy of deceased Covid-19 patients reveals that the spleen is significantly reduced in size. Reduction in spleen size would be expected in the event that the spleen has emptied its reserve of erythrocytes into the circulation as part of a normal physiological response to anaemia (Dale 2016).

Primate models of Covid-19 (Munster 2020) and human Covid-19 patients have subnormal haemoglobin levels (Chen 2020). Clinical evaluation of almost 100 Wuhan patients reveals haemoglobin levels below the normal range in most patients as well as increased total bilirubin and elevated serum ferritin (Chen 2020). Hyperbilirubinemia is observed in acute porphyria (Sassa 2006) and would be consistent with ineffective erythropoiesis (Sulovska 2016) and rapid haemoglobin turnover. Elevated serum ferritin levels are typical of acute porphyria (Trier 2013) and would be expected upon dissociation of iron from haem. A mechanism by which SARS-CoV-2 might attack the 1beta chain of haemoglobin has been proposed; the product of open reading frame 8 (ORF8) binds to the porphyrin of haem and displaces iron, according to bioinformatics prediction analyses (Liu 2020). The oxygen-carrying capacity of erythrocytes would therefore be compromised by SARS-CoV-2, thereby exacerbating the difficulties already experienced by the patient, in terms of maintaining partial pressure of oxygen in the alveoli (P_aO_2).

While the impact of SARS-CoV-2 targeting of haemoglobin on oxygen content of the blood would therefore be considerable, the author proposes that perhaps of greater concern, are potential ramifications upon homeostatic regulation of haem anabolism. Haem biosynthesis is exquisitely controlled by seven enzyme-controlled reactions proceeding from the first intermediate, aminolevulinic acid (ALA), to haem as the final product. Haem negatively regulates the first step in the pathway by repressing expression of aminolevulinic acid synthase (ALAS). SARS-CoV-2 is predicted to directly interfere with haem production (Liu 2020), and this prediction is supported by empirical evidence of reduced haemoglobin levels in Covid-19 patients (Chen 2020) and in animal models of the disease (Munster 2020). Decreased haem production dampens repression of ALAS, and thereby increases the production of haem precursors, leading to accumulation of porphyrin intermediate metabolites. All of the haem pathway intermediates are potentially toxic (Sassa 2006). During an attack of acute porphyria, ALAS is induced 2006) and this perturbation continues until sufficient haem synthesis is restored.

Phenotype of SARS-CoV-2 porphyrin excess is hypothesised to mimic extreme lead poisoning; both as examples of acquired acute porphyria. Overproduction of haem precursors - aminolevulinic acid (ALA) and porphobilinogen (PBG), in particular – manifests life-threatening attacks (Pischik 2015) with neurovisceral symptoms (Sassa 2006), including: abdominal pain (85-95% cases), vomiting (43-88%), constipation (48-84%), muscle weakness (42-60%), mental symptoms (40-58%), pain of the limbs, head, neck and chest (50-52%), hypertension (36-54%), tachycardia (28-80%), convulsion (10-20%), sensory loss (9-38%), fever (9-37%), respiratory paralysis (5-12%) and diarrhoea (5-12%). Neurotoxicity of aminolevulinic acid accounts for the plethora of neurovisceral symptoms and, interestingly, there is considerable overlap between neurovisceral complaints of ALA excess and extra-pulmonary symptoms of critical Covid-19 patients. Extra-pulmonary symptoms of Covid-19 are significant but under-estimated, including gastrointestinal symptoms (Poggiali 2020), which news reports suggest may affect in the region of 50% Covid-19

patients. Neurological problems also appear to be overlooked by the hyper-focus on respiratory symptoms (Zhao 2020). Of 214 Covid-19 patients, 36.4% experienced neurological manifestations including: headache, dizziness, acute cerebrovascular incidents and impaired consciousness (Mao 2020). Loss of autonomic control of breathing has also been reported and autonomic neuropathy is a clinical feature of acute porphyria (Laiwah 1985). Neuropsychiatric symptoms of Covid-19 may be downstream of irregularities in haem metabolism. SARS-CoV-2 would not be the first known virus to alter porphyrin metabolism; hepatitis C virus (Hep C) and human immunodeficiency virus (HIV) infection lead to a non-acute form of porphyria (Blauvelt 1996).

In summary, the first part of the current hypothesis is that critical Covid-19 patients are experiencing a form of acquired acute porphyria; the second part is that treating critical Covid-19 patients with ALA synthase inhibitors may ameliorate extra-pulmonary symptoms of the disease. Diagnosis by urinalysis of porphyrin metabolites would provide a straightforward confirmation or negation of the current hypothesis; ALA urinary excretion of 25-100 mg/d or PBG urinary excretion of 50-200 mg/d is typical of acute porphyria (Sassa 2006). Current therapeutic interventions licensed for treatment of porphyria include: (i) blood transfusion (erythropoietic porphyria), (ii) glucose, (iii) intravenous haematin; and, (iv) chloroquine. Chloroquine induces the release of tissue-bound porphyrins; the initial event following chloroquine administration to porphyria cutanea tarda (PCT) patients is a release of bound hepatic porphyrin and its rapid elimination (Scholnick 1973). Chloroquine is also a known zinc ionophore (Xue 2014) and aids zinc uptake; chloroquine may indirectly facilitate zinc insertion, catalysed by ferrochelatase, into excess protoporphyrin. Zinc protoporphyrin is less toxic than free protoporphyrin.

The author concedes that conclusions of the current brief communication are, unconventionally, extrapolated from singular studies for which the results await tests of reproducibility. The reader's grace is implored in understanding that the pandemic is a rapidly evolving situation and the purpose of the current communication – to suggest possible adjuvant therapies at the peak of the crisis – would be negated by lengthy peer review. Finally, if haemoglobin-targeting is an important component of the Covid-19 pathophysiology, susceptibility to the disease may differentiate according to ethnicity – depending upon the particularities of haemoglobin-targeting. South East Asian ethnicities have higher prevalence of haemoglobin E (Ha 2019); epidemiologically, this would be analogous to maintenance of sickle cell heterozygosity in West African ethnicities as a selective advantage in protecting against malaria.

Conflict of interest

None declared

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