



COVID-19 INFECTION AND PROTEIN MALABSORPTION: IS THIS ACQUIRED HARTNUP'S DISEASE?

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ABSTRACT

Many severe Covid-19 patients develop gastrointestinal (GI) disturbances. Understanding the mechanism of GI disturbances is warranted for exploring better clinical care for Covid-19 patients. The Hartnup's disease is a rare autosomal recessive inherited disease. Hartnup's disease includes neurologic manifestations, or psychiatric symptoms, together with the GI disturbances which are described in severe Covid-19 cases. It is hypothesized that Covid-19 may share a pathophysiological mechanism with the Hartnup's disease. It is hypothesized that SARS-CoV-2 spike protein, binding to intestinal angiotensin-converting enzyme 2 (ACE2), negatively regulates the absorption of neutral amino acids, and this could explain gastrointestinal (GI) and systemic disturbances in Covid-19. Amino acid supplements could be recommended. We are reporting 3 cases of post-acute Covid-19 syndrome (PASC) who were found to have low Serum Creatinine values, diarrhea, and neuropsychiatric symptoms, had protein malabsorption and responded to supplementations of amino acids, with tryptophan and niacin. Thus, we would like to go with the existing hypothesis that Covid-19 may share a pathophysiological mechanism with the Hartnup's disease.

KEYWORDS: Covid-19, diarrhea, malnutrition, low blood urea nitrogen and serum creatinine, acquired Hartnup's disease, amino acid supplements.

INTRODUCTION

Approximately 30% of acute Covid 19 disease have persistent symptoms.^[1] and are being given the diagnosis as Long Covid, post-acute Covid-19 syndrome (PACS), or post-acute sequelae of Covid-19 (PASC). These 'long haulers' have lingering disease, either due to direct viral invasion, immune and inflammatory perturbations or hidden viral reservoirs that lead to abnormal metabolism and mitochondrial dysfunction, imbalance in renin angiotensin system or altered microbiome.^[2] A large number of patients with severe Covid 19 develop gastrointestinal (GI) disturbances, (even in the absence of cough and dyspnea) which include diarrhoea, anorexia, nausea, vomiting, stomach discomfort, and gastrointestinal bleeding, of which diarrhoea could range from 2.0 to 47.9%.^[3] Understanding the mechanism of GI disturbances is warranted for exploring better clinical care for Covid-19 patients.

The Hartnup disease is a rare inherited disease, in which the Angiotensin Converting Enzyme 2 receptor (ACE-2) dependent trafficking of B⁰AT1—a sodium dependent transporter of neutral amino acids—is genetically defective. Notably, Hartnup disease includes cutaneous

alterations, neurologic manifestations, or psychiatric symptoms, frequently described in severe Covid-19 cases, together with the GI disturbances. It is hypothesized that Covid-19 may share a pathophysiological mechanism with the Hartnup disease.^[4]

MATERIAL AND METHODS

Out of approximate 3500 Covid-19 patients from March 2020 to July 2021 admitted to a tertiary care center, and having about 100 cases of PASC, we are reporting 3 cases of PASC who were found to have low Blood Urea Nitrogen (BUN) and Serum Creatinine values. It was decided to measure their protein intake, as absorbed protein from gut. Biochemical methods for estimating protein intake are based on the concept that nitrogen-containing products of protein in diet plus the products arising from endogenous protein are excreted as either urea or non-urea nitrogen (NUN). This formulation is based on the fact that the urea is the principal end product of amino acid degradation and, hence, the urea appearance rate (or net urea production) is parallel to protein intake. The urea nitrogen appearance (UNA) rate is measured as the amount of urea excreted in urine plus

the net amount accumulated in body water.^[5] The UNA was calculated from 24 hours urinary urea excretion using following equation.

The urea nitrogen appearance, U, equals the urine urea nitrogen + the non-urea nitrogen (weight in kg X 0.031 g nitrogen/kg/day). Calculated Protein Intake is urine nitrogen excreted in grams/day + (weight in kilograms X 0.031 g nitrogen/kg/day) multiplied by 6.25.^[6]

Case 1: 55 years female, original weight 70 kg, had Covid-19 related acute kidney injury, S. Creatinine was maximum up to 3.2 mg/dl, not requiring dialysis, recovered her kidney function and then was found to have BUN of 8 mg/dl and Serum Creatinine of 0.2 mg/dl with a weight of 60 kg. Her total serum proteins were 4.7 gm/dl with S. Albumin of 2.5 gm/dl. She had tracheostomy and was on nasogastric tube feeding with protein powder supplementations of 100 grams per day. She used to have loose motions off and on, and protein supplements would be adjusted accordingly. She used to be irritable at times and have neuropsychiatric symptoms, requiring pharmacological assistance. Her UNA was 26 gram with protein intake through formula NJ feed of 100 gm/day.

Case 2: 41 years male, weighing 110 kgs, having severe lung involvement post Covid-19, requiring ECMO (Extra Corporeal Membrane Oxygenation), had loose motions while on nasogastric formula feeds with protein intake of 120gm per day, and psychological issues. He was referred for decreased urine output and had low BUN of 7 mg/dl and S. Creatinine value of 0.38 mg/dl. His UNA was 39 grams. His S. Proteins and S. Albumin were 5.9 and 2.7 gm/dl respectively.

Case 3: 45 years old female, weight 60 kg, continued to be on ventilator post Covid-19, and developed loose motions. She also had psychiatric manifestations, BUN of 6 mg/dl and S. Creatinine level of 0.25 mg/dl. She had UNA of 40 grams in spite of getting proteins of 100 grams per day, with S. Proteins and S. Albumin of 5.1 and 2.4 gm/dl.

RESULTS

Based on this hypothesis that we were dealing with acquired Hartnup's disease situation, all patients were started on intravenous amino acid infusions of LAMINO NEPHRO® (La Renon Healthcare Pvt Ltd, La Renon Corporate House, Behind Rajpath Club, Kensville Road, Opp. Infostretch Building, Off S.G. Highway, Ahmedabad, Gujarat 380059), 7% 250 ml per day gradually increasing to 1 liter per day. This provided total nitrogen content of 10.8 gm/L, total amino acids of 70 gm/L, and tryptophan of 1.9 gm/l. In addition, oral niacin was started at 1000 mg/day. This resulted in improvement in the neuropsychiatric symptoms, diarrhea gradually settled, and BUN improved to 20-25 mg/dl and S. Creatinine levels improved to 0.7-1.0 mg/dl, suggesting improved protein metabolism.

DISCUSSION

All the patients had PASC, were supplemental proteins through tube feeding, at a dose of proteins of >1gm/kg, which would usually be considered sufficient. But in all 3 cases, further investigations were necessary due to the finding of low S. Creatinine values. It was found that all patients UNA values were low, suggesting that the absorption of proteins from the gut was inadequate. This poor gut absorption of proteins was the cause for low S. Creatinine values. This was combined with diarrhea and neuropsychiatric manifestations.

It has been hypothesized that severe acute respiratory syndrome coronavirus 2 (SARS-Co-V-2) binding to ACE2 in the small intestine may cause functional changes of enterocytes and start the innate immune response, whose symptoms may mimic Hartnup's disease or disorder, or also known as pellagra like dermatosis, is an autosomal recessive metabolic disorder, affecting the absorption of nonpolar amino acids, especially tryptophan which is converted to serotonin, melatonin and niacin. Individuals with Hartnup disease who do not develop symptoms will usually not require any treatment.

In normal subjects, urea appearance is usually equal to urea excretion. In renal failure, turnover time of urea is prolonged. In subjects with normal renal function, urea excretion may reduce and is taken as reflection of urea production.^[7] This was taken as basis for measuring UNA. The absorption of neutral amino acids which is negatively regulated in Covid-19 patients lead to neutral amino acids (and probably small proteins) accumulation in the intestinal lumen, promoting diarrhoea with protein malabsorption, microbiota changes, and immune defects. In malnourished patients or conditions of intestinal amino acid malabsorption, as in the Covid-19 (and Hartnup's disease patients), the adaptive immune response cannot be effectively initiated because the absorption of essential energy substrates is impaired by SARS-CoV-2 binding to ACE2. Meanwhile, the diversion of energy substrates to the maintenance of the immune system, in addition to reduced oxidized form of Nicotinamide Adenine Dinucleotide (NAD⁺) synthesis, causes insufficient protein synthesis and energy production in skeletal muscle and brain. Similarly, the reduced serotonin synthesis may affect brain function and explain some neurological and psychiatric symptoms in Covid-19. Based on this hypothesis, all patients were given IV amino acids, tryptophan and oral niacin at 100 mg per day. This resulted in clinical and biochemical improvement. In some instances, during a symptomatic episode, treatment with nicotinamide may be recommended.^[8] Hartnup patients have tryptophan deficiency due to increased urinary excretion which decreases the availability of this amino acid for the synthesis of niacin. Hence tryptophan supplementation is also necessary.

Since there was gradual improvement in diarrhea and neuropsychiatric symptoms, we would like to go with the existing hypothesis (4) that Covid-19 may share a pathophysiological mechanism with the Hartnup disease in terms of protein malabsorption and diarrhea and Covid-19 patients with GI and neuropsychiatric symptoms and suggestion of malabsorption described in the present article should be treated like Hartnup's disease.

CONCLUSION

We have presented three cases of post-Covid-19 PACS, who developed malabsorption and diarrhea and could have acquired Hartnup's disease secondary to Covid-19 infection sequelae. The appropriate treatment resulted in favorable clinical outcome.

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