The Journal of Medical Research

***Case Report***

JMR 2022; 8(3):89-92
May- June
ISSN:2395-7565

www.medicinearticle.com
Received:14-04-2022
Accepted:08-06-2022

# 'The Long and Short of COVID-19'

***Hemant Mehta[1], P Swapna[2], Prakash Jiandani[2], Vasant Nagvekar[3], Girish Soni[4]***

*[1] Department of Nephrology, Lilavati Hospital and Research Center, Bandra Reclamation, Mumbai 400050, India*
*[2] Department of Critical care Medicine, Lilavati Hospital and Research Center, Bandra Reclamation, Mumbai 400050, India*
*[3] Department of Infectious Disease, Lilavati Hospital and Research Center, Bandra Reclamation, Mumbai 400050, India*
*[4] Department of Neurology, Lilavati Hospital and Research Center, Bandra Reclamation, Mumbai 400050, India*

## Abstract

COVID-19 illness is self-limiting illness in majority of patients, but some patients continue to have or develop new medical issues four weeks after suffering from the infection (proven or presumed), and have been labelled as Long Covid, which depicts the consequences of COVID-19.The duration of Long Covid beyond 4 weeks is unknown. We are reporting a case of a young female who presented with encephalopathy which was due to asymptomatic COVID-19 infection suffered in the past. Could this be a Long Covid syndrome? How was the diagnosis of Covid encephalopathy suspected and investigated, with its treatment and review of relevant literature is described

**Keywords:** COVID 19, SARS-CoV-2 Infection, Long Covid, Covid Encephalopathy, Hyponatremia, Anti-SARS-CoV-2 Antibody.

**INTRODUCTION**

Coronavirus Disease 2019 (COVID-19), usually a self-limiting illness, lasting for 7-14 days, may cause persistent symptoms beyond 4 weeks or new onset of symptoms involving many organ systems, which are later recognized as sequelae of preceding COVID-19 infection. This can also happen to those who have never had symptoms of COVID-19 but have evidence of having suffered from the disease, by demonstrating Covid nucleocapsid antibody positivity. As per Centre for disease control (CDC), post-Covid (also known as Post-Acute Sequel of Covid (PACS or PASC) [1]. conditions are a wide range of ongoing or new health issues more than four weeks after COVID-19 infection. The National Institute for Health and Care Excellence (NICE) has a different definition for Long Covid, happening beyond 12 weeks. Common long Covid symptoms include fatigue, breathlessness, anxiety, depression, palpitations, chest pain, myalgia, change of taste or smell etc. It can be multi organ effects, affecting heart, lung, kidneys, skin, brain etc. The females, elderly, and patients who had more than 5 symptoms at the time of active COVID-19 infection are more predisposed to develop Long Covid [2]. Some of these PASC patients develop extreme tiredness and sleep issues, and the symptoms worsen if they try to do more activities. These symptoms may be ascribed to the preceding COVID-19 illness but could have an overlap with another disease condition called as myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) and both of these conditions could be confused as both of these conditions begin with viral 'viral' infection.

We are reporting a case of a young female who presented with encephalopathy due to asymptomatic COVID-19 infection suffered in the past. Could this be a Long Covid syndrome? How was the diagnosis of Covid encephalopathy suspected and investigated, with its treatment and review of relevant literature is described.

**CASE REPORT**

20 years old female with no comorbidities was admitted in ICCU in February 2021. At this time, patient had no evidence of respiratory excretion of COVID-19 virus, her RT-PCR and CBNAAT for COVID-19 were negative. There was no h/o COVID-19 pneumonia. She presented with occipital headache and fever of 8 days duration. On admission, she had urinary retention, and drained 1400 cc urine after catheterization. Renal biochemistry was normal except for serum sodium at 130mEq/L, which reduced to 117mEq/L on days 3. She became drowsy, and meningitis was suspected. Initial MRI of brain was normal.

***Corresponding author:**
***Dr. Hemant Mehta***
Department of Nephrology, Lilavati Hospital and Research Center, Bandra Reclamation, Mumbai 400050, India
Email:
drhemantmehta@gmail.com

She had acute, profound, severely symptomatic, hypoosmolar, euvolemic hyponatremia. To find out exact cause of hyponatremia (syndrome of inappropriate antidiuresis, SIADH v/s cerebral salt wasting, CSW), simultaneous urinary osmolality, electrolytes, urea nitrogen, creatinine, phosphorus and uric acid with serum osmolality, BUN, S. Creatinine, S. Phosphorus, S. Uric acid were sent to calculate fractional excretion (Fe) of sodium (Na), uric acid (UA or urate), phosphorus (Pi) and urea (U). It showed urinary Na (UNa) 80, FeNa 0.7, FeUA 12.11, FePi 46.8 and FeU 63.3 favouring cerebral salt wasting over SIADH.

As the salt wasting of central origin (cerebral) became obvious, MRI of brain was repeated to see if any new changes are visible. Second MRI showed T2 hyper intensities bilaterally symmetrical in pons with extension in medulla, periaqueductal area, mid brain, hypothalamus and sub thalamus areas s/o brain stem encephalitis [Figure 1].

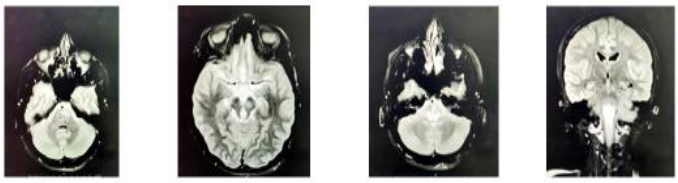

**Figure 1:** Second MRI showing T2 hyperintensities bilaterally symmetrical in pons with extension in medulla, peri-aqueductal area, mid brain, hypothamus and subthalamus areas, suggestive of brain stem encephalitis

Cerebrospinal fluid (CSF) studies were done twice [Table 1], which showed lymphocytic predominance both times with decreasing trend in CSF cells and proteins and negative BioFire ® assay for bacterial panel. CSF Immunoglobulin G (IgG) was checked second time was raised (not done earlier) suggesting immunological process.

**Table 1:** CSF picture

| Parameter | 7.02.21 | 15.02.21 |
|---|---|---|
| Cells | 90 (L +++) | 40 (L +++) |
| Proteins | 152.7 | 126 |
| Sugar | 49 (RBS 95) | 108 (RBS 193) |
| LDH | 77 | 70 |
| Biofire | Negative | Negative |
| IgG | --- | 150 (Increased) |

To find out the cause of encephalitis, various laboratory and immunological tests were done. None of the tests could show the cause towards it being infective. There was no obvious evidence for any metabolic cause and we could not document any toxin in the urinary toxic screen. Anti-N-methyl D-aspartate (NMDA) receptor antibodies were negative. COVID-19 antibody (Serum Anti-SARS-CoV-2 Antibody) was also checked. The proof of it being inflammatory was obtained by documenting positive Anti-SARS-Co-V-2 antibody in the serum, with a titer of 15.63 (Negative <0.8). CSF Anti-SARS-CoV-2 Antibody titer was also significantly high at 28, suggestive of post COVID-19 encephalitis.

She was treated with intravenous immunoglobulins (IVIg), 2 gm/kg, over 5 days followed by Injection Rituximab 375mg/$m^2$ body surface area. Prior to the second dose of Rituximab, a week later, she developed fever and the blood culture grew Klebsiella pneumonia. Appropriate antibiotics were administered followed by second dose of Rituximab. She responded to the treatment, recovered gradually and was discharged from the hospital after 3 months and is fine after 1 year.

**DISCUSSION**

Our patient presented with symptoms suggestive of encephalopathy. She had mild, moderately symptomatic hyponatremia on admission, which worsened to profound and severely symptomatic hyponatremia. The investigations revealed that she had cerebral salt wasting as the cause of hyponatremia. This gave the clue to evaluate further and the MRI of brain was repeated, followed by repeat CSF study. The IgG level in CSF was done suspecting it to be immunological process, and it was positive. Hence COVID-19 nucleocapsid antibody was tested in serum and CSF, and both were positive, though she never had COVID-19 infection in the past, and COVID-19 RT PCR on admission was negative. Her presentation of urinary retention, with hyponatremia (Cerebral / renal Salt Wasting (C/RSW)) raised the suspicion of a neurological cause which led to the correct diagnosis.

This condition of C/RSW was reported in 1950, whereas SIADH was reported by Schwartz and Bartter in 1957 [3,4]. It took 30 years for SIADH to be recognized as a disease. It stated that natreuresis in C/RSW is due to renal salt wasting state. This was contrary to the present knowledge that disorders of sodium are related to water and not to salt. In C/RSW, the primary event is a brain disorder. It leads to renal tubular natreuresis, accompanied by aquaresis, causing intravascular volume depletion. This state of relative 'dehydration' is a trigger for renin secretion, the renin, angiotensin, aldosterone system (RAAS) is activated leading to the secretion of anti-diuretic hormone (ADH). ADH level could be either appropriate or inappropriate for the degree of low sodium level, and accordingly patients have R/CSW or SIADH, and patients are either dehydrated or well hydrated respectively. Measurement of fluid status is essential to clinically differentiate between the two conditions. Estimation of plasma renin activity or serum aldosterone level does not aid in the diagnosis. Similarly, a central venous pressure (CVP) line insertion becomes necessary to differentiate between hypo and euvolemic states. However, caution must be exerted to determine volume status in young patient who have normal heart function and head injury, as their CVP would be low even during healthy conditions.

Hypouricemia in C/RSW [5]. and an approach to hyponatremia in the present case Under physiological condition, uric acid is reabsorbed by renal tubules whereas urea is both secreted and reabsorbed. This process of reabsorption of uric acid and urea is linked to sodium reabsorption, which is defective in R/CSW. This results in hyperuricosuria (high fractional excretion of urate ($FE_{urate}$), and this defect persists even when sodium level is corrected with normal saline [6]. As opposed to this, sodium levels will fall further with saline infusion in SIADH and uric acid level will return to normal with sodium correction in SIADH.

Depending on $FE_{urate}$ values, hyponatremia can be differentiated, as <4% (volume depletion, Addison disease, edematous state, congestive heart failure, cirrhosis, nephrotic syndrome), 4-11% (psychogenic polydipsia, reset osmostat) and >11% (SIADH, C/RSW). If the $FE_{urate}$ level remains > 11% in spite of correction of sodium, it is in favour of C/RSW. However, if $FE_{urate}$ falls <11 % with normonatremia, it could be SIADH or hydrochlorthiazide use.

C/RSW can be differentiated from SIADH by fractional excretion of phosphate also, it is high in case of C/RSW [7]. In true case of salt wasting, normal saline infusion over 36 hours generates dilute urine with correction of hyponatremia, whereas hyponatremia may worsen with normal saline in SIADH [5]. We treated our patient with normal saline, and over 3-4 days, serum sodium was corrected and remained stable.

**COVID-19 encephalopathy**

The proof of COVID-19 causing encephalitis was obtained by demonstration of SARS-CoV-2 virus in the CSF by genomic sequencing at Ditan hospital in Beijing [8]. where 31.8% of the hospitalized 509

patients had COVID-19 encephalitis. The demography of these patients showed that those above 66 years old were more likely to have COVID-19 encephalitis than those less than 55 years old, males were more predisposed than females, encephalitis patients had 6 days' time from onset of symptoms to hospitalization compared to 7 days for those who did not have encephalitis. Pre-existing cancer, cerebrovascular disease, chronic kidney disease, diabetes, dyslipidemia, heart failure, hypertension or past history of any neurological disorder were found as risk factors for COVID-19 encephalitis [9].

Our patient was young, female and had no risk factors. Another study [10]. found 28% incidence of encephalopathy as presenting feature among 817 patients with median age of 78 years.

There has been reports of demonstration of SARS-CoV-2 antibody in the CSF of two patients [11]. normal CSF cells, and increased protein and sugar levels. CSF Immunoglobulin G (IgG) index was normal suggesting no intrathecal IgG production at isoelectric focussing. These cases were attributed to COVID-19 encephalopathy.

So, as per the available literature, patients with COVID-19 infection can present with encephalopathy and may have elevated immunoglobulin in the CSF. Our patient had no active or history of past COVID-19 infection, and presented with encephalopathy. Past COVID-19 infection, was confirmed by presence of COVID-19 antibodies in serum and CSF and elevated IgG level in the CSF.

**Autoantibodies in CSF of COVID-19 patients**

COVID-19 virus is rarely detected in the CSF. Elevated IgG level and presence of Anti-SARS-CoV-2 Antibody in the CSF of our patient was similar to the findings of autoantibodies detection in another study [12]. of 11 patients who presented with varied neurology problems, the cause of which was unknown. Their CSF showed high levels of anti-neuronal and anti-glial antibodies and its confinement to specific immunofluorescence patterns was considered remarkable in their analysis. Though patients had IgG autoantibodies targeting neuropil of basal ganglia, hippocampus or olfactory bulb, astrocytic protein or endothelium of medium-sized blood vessels, and demonstration of IgG in the rat's brain, it was not considered adequate evidence and one would need more patients to correlate clinical and pathological sequences.

It can be hypothesized that COVID-19 virus triggers autoimmune response, leading to neurological symptoms and there could be a role for immunotherapy targeting the cerebral fiber network around basal ganglia, and the clinical response could be a proof that autoantibodies are responsible for COVID-19 encephalopathy.

**Post-COVID Conditions/ "post-acute COVID-19 syndrome**

World Health Organization (WHO) coined the term 'Post Covid condition' and defined it as a situation in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time" [13].

Types of Post-COVID Conditions [14]. (Long Covid) PASC (as defined above) or 'Long Covid' can present as following situations:

1) Multi-organ effects of COVID-19: affecting brain, kidneys, lung, heart and skin and causing immunological disorder, like in our patient. PASC has also been responsible to cause multi system inflammatory syndrome in children as well as adults.
2) Effects of COVID-19 Treatment or Hospitalization: these include a) post intensive care syndrome (PICS) and b) post-traumatic stress disorder (PTSD).

PASC can have multiple overlapping causes, which could be triggered by SARS-CoV-2 virus and injure one organ. This would then lead to either multiple organs, or remain hidden in some organs including brain, only to be re-activated at a later date under certain immunological deregulation, leading to interaction with host's existing bacterial or viral flora (micro-biome dysbiosis). This can lead to thrombosis and coagulopathy. It can also cause incoordination between brain stem and vagus nerve. Immune cells can get primed by SARS-CoV-2 virus and propagate autoimmunity. This could happen due to molecular mimicry between SARS-CoV-2 virus and existing proteins in the infected patient [15].

**CONCLUSION**

The patient had COVID-19 encephalopathy, though there was no history of COVID-19 infection. She developed C/RSW secondary to encephalopathy. The COVID-19 encephalopathy was diagnosed based on positive COVID-19 antibody (Anti-SARS-CoV-2 Antibody) in plasma and serum simultaneously and elevated IgG levels in CSF. She was treated with IVIg and rituximab, responded and recovered gradually. She was discharged after 3 months of hospitalization. This case shows that COVID-19 infection can have long term sequelae even in patients who did not have history or symptomatic COVID-19 infection in the past. Strong suspicion and appropriate work up and treatment can lead to therapeutic recovery. In our opinion, this case fits in to the WHO definition of post COVID-19 condition.

**Conflicts of interest**

None declared.

**Financial support**

None declared.

**REFERENCES**

1. Fauci Introduces New Acronym for Long COVID at White House Briefing - Medscape - Feb 24, 2021.
2. Collins F. Predicting Long Covid Syndrome with help of a smartphone app, NIH Director's blog, March 2021.
3. Peters JP, Welt LG, Sims EA, Orloff J, Needham J. A salt-wasting syndrome associated with cerebral disease. Trans Assoc Am Physicians. 1950;63:57-64.
4. Schwartz WB, Bennett W, Curelop S, Bartter FC. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am J Med. 1957;23(4):529-42.
5. Bitew S, Imbriano L, Miyawaki N, Fishbane S, Maesaka JK. More on Renal Salt Wasting Without Cerebral Disease: Response to Saline Infusion. Clin. J Am. Soc. Nephrol. 2009;4(2)309-15.
6. Maesaka JK, Imbriano LJ, Miyawaki N. Determining Fractional Urate Excretion Rates in Hyponatremic Conditions and Improved Methods to Distinguish Cerebral/Renal Salt Wasting From the Syndrome of Inappropriate Secretion of Antidiuretic Hormone. Front. Med. 2018; 5:319.
7. Nickson C. SIADH v/s CSW, Life in the fast lane, 03 November. 2020.
8. Xiang P, Xu XM, Gao LL, Wang HZ, Xiong HF, Li RH, *et al*, First Case of 2019 novel coronavirus disease with encephalitis. ChinaXiv. 2020; T202003:00015.
9. Liotta EM, Batra A, Clark JR, Shlobin NA, Hoffman SC, Orban ZS, *et al*. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol. 2020;7(11):2221-30.
10. Kennedy M, Helfand BKI, Gou RY, Gartaganis SL, Webb M, Moccia JM, *et al*. Delirium in Older Patients With COVID-19 Presenting to the Emergency Department. JAMA Netw Open. 2020;2:3(11):e2029540.
11. Andriuta D, Roger PA, Thibault W, Toublanc B, Sauzay C, Castelain S, *et al*. COVID-19 encephalopathy: detection of antibodies against SARS-CoV-2 in CSF. J Neurol. 2020;267(10):2810-11.

12. Franke C, Ferse C, Kreye J, Reincke SM, Sanchez-Sendin E, Rocco A, *et al*. High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms. Brain Behav. Immun. 2021;93:415-19.
13. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021.
14. Post COVID Conditions (e.g. Long COVID), 26 February 2021.
15. https://www.idsociety.org/covid-19-real-time-learning-network/disease-manifestations--complications/post-covid-syndrome/
16. Proal A, VanElzakker Michael B. Long COVID or Post-acute Sequelae of COVID-19 (PASC): An Overview of Biological Factors That May Contribute to Persistent Symptoms. Front. Microbiol. 2021;12.