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Case Report

SARS CoV2 infection in a young subject affected by arginosuccinate synthase deficiency: A case report of epilepsy worsening

N. Vitturi [a,*], L. Lenzini [b], F. Francini-Pesenti [c], G. Gugelmo [c], A. Avogaro [a]

[a] University of Padova, Department of Medicine-DIMED, Division of Metabolic Diseases, University Hospital, Padova, Italy
[b] University of Padova, Department of Medicine-DIMED, Emergency and Hypertension Unit, University Hospital, Padova, Italy
[c] University of Padova, Department of Medicine-DIMED, Division of Clinical Nutrition, University Hospital, Padova, Italy

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SUMMARY

We describe a case of a 21 years old woman affected by Citrullinemia type 1- Arginosuccinate Synthase deficiency (ASSD)-who underwent a SARS CoV2 infection during the first phase of pandemic burst in Italy. She had no symptoms of infection nor a metabolic crisis.

After recovery from SARS CoV2, she experienced a worsening in their epilepsy despite therapy, with one/two crisis a week.

1. Case Report

The case is a 21 years old woman affected by ASSD (OMIN 215700). The diagnosis was made in the neonatal period with a metabolic coma due to hyperammonemia in the first days of life. She had a twin sister deceased when she was sixth years old due to a metabolic crisis.

She experienced several episodes of metabolic crisis in the first ten years of life; thereafter she presented a more stable clinical picture, with no acute metabolic hyperammonemia crisis but with episodes of myoclonic epilepsy (maybe linked to a previous metabolic damage) and behavioral disturbances (aggressive episodes directed to her family members and herself). Her therapy for the metabolic disease consists of sodium benzoate, sodium phenylbutyrate (switched in 2019 with glycerol phenylbutyrate), and arginine; a low protein diet (25 g/die of total protein (0.47 g/kg/die), of them 20 g/die (0.36 g/kg/die) from natural protein and 5 g/die from Essential Amino Acid supplements; energy 1200 Kcal/die (23 kcal/kg/die)); drugs for epilepsy and behavioral problem (Levetiracetam switched to brivaracetam and clonazepam in 2019, methylphenidate, quetiapine).

In September 2019 her metabolic profile was normal, with ammonium (42 μmol/l; normal range 16–53) and glutamine (690 μmol/l; normal range 359–748) in the normal range. The plasma level of levetiracetam was in the therapeutic range. She experienced no epileptic crisis during the last two years.

In March 2020 she had a diagnosis of SARS CoV2 infection (a positive nasopharyngeal/oropharyngeal swab) during a screening for strict contact with a positive person. She had no symptoms of viral infection (she referred no fever, cough, dyspnea, thoracic discomfort, myalgias). Her mental status was stable, without acute neurological signs or behavioral changes.

Due to the pandemic, we were not able to obtain a blood sample to monitor her biochemical metabolic profile during the infection, so we decided not to modify pharmacological therapy or diet (we did not stop protein intake or use emergency diet), but to make only a strict clinical follow up.

After two weeks, the patient had a negative PCR for SARS CoV2 in nasopharyngeal/oropharyngeal swab and we also obtained a blood sample. The metabolic profile was normal, with plasma ammonium of 33 μmol/l (normal range 16–53) and a plasma glutamine of 527 μmol/l (normal range 359–748). Changes in plasmatic amino acid levels are summarized in Table 1.

After almost two years from the last epileptic crisis, despite the optimal metabolic control after the SARS CoV2 infection, in April she started to experience an episode of atony, loss of consciousness, and sphincter release. A new crisis occurred 20 days later with atony followed by a tonic-clonic seizure. On that occasion, the plasma ammonium was 23 μmol/l (normal range 16–53). An electroencephalogram was performed in May, showing epileptiform anomalies with diffused projection, with predominantly right frontal expression, accentuated by hyperpnea. The neurologist changed her drug therapy introducing

* Corresponding author.
E-mail address: nicola.vitturi@aopd.veneto.it (N. Vitturi).

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Table 1
plasma amino acids concentration before and after SARS CoV2 infection.

Aminoacid (μmol/L)	Before COVID	After COVID	Normal Range
Methionine	16	**14**	15–49
Cystine	41	**22**	35–63
Valine	**123**	**114**	143–352
2 Aminobutyrate	11	9	8–34
Citrulline	**2884**	**2233**	17–55
Proline	168	192	108–451
Glycine	149	152	147–395
Alanine	**614**	**740**	239–543
Lysine	140	130	111–248
Histidine	74	69	57–101
Ornithine	54	55	40–165
Phenylalanine	**36**	41	39–74
Tyrosine	**23**	**32**	35–84
Leucine	**59**	**61**	78–160
Isoleucine	43	34	34–84
Arginine	**100**	**102**	15–87
Taurine	**14**	**29**	35–146
Aspartate	3	5	1–13
Threonine	**192**	163	72–168
Hydroxyproline	**17**	15	2–15
Serine	**65**	**60**	87–151
Asparagine	40	36	33–67
Glutamate	23	45	1–57
Glutamine	690	527	359–748

lamotrigine.

While the metabolic status remained unchanged (in September plasma amino-acids values were normal; in October-shortly after a tonic-clonic seizure- the ammonium was 17 μmol/l), epileptic crises persisted despite therapy, with a frequency of one/two crisis in a week with both absence or seizure, associated with an aggressive behavior.

2. Discussion

Despite the widespread diffusion of SARS CoV2, there are only a few reported infections in patients with inherited metabolic diseases [1,2]. The reason for the low prevalence among this population is not known, but it may be due to the attention given to social distancing among these patients and their families.

The risk of severe SARS CoV2 infection is unknown in patients affected by IMDs. We know that patients with UCD are at great risk of metabolic decompensation when affected by viral infection: the augmented catabolism associated with gastrointestinal symptoms (frequently during viral infections) makes them prone to hyperammonemia. Usually, for milder infection, modifications of the nutritional regime (i.e. stop of protein intake and hypercaloric nutrition with carbohydrates and lipids to overcome catabolism) are sufficient to control the disease; for more severe form, or when oral food intake is impaired, hospitalization with drug therapy (*endo*-venous infusion of arginine, nutrition and ammonium scavengers) is needed.

Luckily, our patient experienced no symptoms of acute infection, and she was able to correctly follow her usual drug therapy. While higher energy consumption is described in the literature [3] during severe COVID, data in milder form are lacking. Our patient never showed a hypercatabolic state, as she didn't show any neurological impairment or biochemical sign of metabolic decompensation (both ammonium and glutamine were normal) even following her usual, low protein, diet.

SARS CoV2 symptoms may be multisystemic: fever, cough, and myalgias are frequent in the first, viral replicative phase, often associated with gastrointestinal symptoms (nausea, vomiting, and diarrhea); dyspnea and respiratory insufficiency, leading to multi-organ failure, are described in the later phase of infection (the cytokines storm phase) [4]. As people with important comorbidity are more at risk of complication (which can lead the event to death) [5] during SARS CoV2 infection, an early hospitalization must be considered for UCD patients showing signs of worsening (often quickly evolving to severe form), because an evolving infection may lead to metabolic decompensation.

In the case of moderate-severe COVID, it is also important to remember that the drug therapy with a high dose of steroid [6] may lead to hyper catabolism and subsequently hyper-ammonium state, so an accurate nutritional balance must be obtained. It must be also considered that UCDs are a risk factor for thrombosis [7] that is a major complication of COVID [8].

On the other hand, it has to be considered that patients with Urea Cycle Disorders (UCDs) are usually young and, in the general population, young people show less frequent symptoms of acute SARS, thus a strict clinical and metabolic monitoring may be enough in the milder form.

The effect of COVID on epilepsy is even less clear. However, data from literature showed that seizure is more frequent during the acute phase of infection, with EEG showing frontal sharp waves [9] and COVID seems to be a risk factor for seizure worsening, as depicted from Italian multicenter data during the first phase of pandemic [10]. Our patient showed a marked, persistent worsening in frequency and severity of seizures, even long-lasting after acute infection and not linked to metabolic derangement. We do not know if the seizure occurrence in our COVID-19 patient may be merely coincidence or is due to viral infection. There are many hypotheses for seizure during the acute phase of SARS CoV2 infection [11], but our patient's seizures worsened after the recovery from COVID. Data from literature suggest a possible link between depression and related difficulties in emotion regulation- worsened during SARS CoV infection [12]- and epilepsy [13,14]; in fact our patient showed an aggressive behavior after COVID.

In conclusion, our case of acute SARS CoV2 infection in a female adult patient affected by Arginosuccinate Synthase deficiency showed that patients with UCDs may experience an asymptomatic infection, both for symptoms related to the virus both for the metabolic crisis. Unfortunately, we have not been able to precisely monitor biochemical data (ammonium, plasma amino acid levels) during the acute phase of COVID.

Moreover, it has not been possible to obtain a cerebral NMR of the case after acute SARS CoV2 infection (due to poor compliance of the patient toward sedation and to the difficult access to hospital facilities due to restrictions for outpatients in Italy) [13].

However, this case strongly suggests that a worsening of neurological complication of UCDs (i.e. seizures) may be observed after the acute phase of SARS CoV2 infection and a long term strict clinical follow up may be needed.

Disclosure

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