Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
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 Inherited 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

ARTICLE INFO

Keywords:
Urea cycle disorders
Inherited metabolic diseases
SARS-CoV2
Epilepsy
Seizures
Metabolic crisis

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 (OMIM 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 glyc erol 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, dysnea, 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...
Molecular Genetics and Metabolism Reports 26 (2021) 100698

Onset of tonic-clonic seizure- the ammonium was 17 μmol/L, lamotrigine.

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          | 35–85        |
| 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      |

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. 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].

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

The authors declare that they have no disclosure.

Funding

No funding.

References

[1] A. Caciotti, E. Procopio, F. Pochiero, S. Falliano, G. Indolfi, M.A. Donati, L. Ferri, R. Guerrini, A. Morrone, SARS-CoV-2 infection in a patient with propionic academia, Orphanet J. Rare Dis. 15 (2020) 206, https://doi.org/10.1186/s13023-020-01563-w.
[2] F. Mercolini, D. Donà, Y. Girtler, K.A. Mussner, P. Bihan, A. Bordugo, G. Molinaro, First paediatric <scp>Covid</scp> – <scp>19</scp> associated death in Italy, J. Paediatr. Child Health (2020), https://doi.org/10.1111/jpc.14994 jpc.14994.
[3] J. Whittle, J. Molinger, D. MacLeod, K. Haines, P.E. Wichmeyer, Persistent hypermetabolism and longitudinal energy expenditure in critically ill patients with COVID-19, Crit. Care 24 (2020), https://doi.org/10.1186/s13054-020-03286-7.
[4] H.K. Siddiqi, M.R. Mehra, COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal, J. Hear. Lung Transplant. 39 (2020) 405–407, https://doi.org/10.1016/j.healun.2020.03.012.

N. Vitturi et al.
[5] X. Zhou, Z. Cheng, D. Shu, W. Lin, Z. Ming, W. Chen, Y. Hu, Characteristics of mortal COVID-19 cases compared to the survivors, Aging Albany. NY 12 (2020), https://doi.org/10.18632/aging.202215.

[6] RECOVERY Collaborative Group, Dexamethasone in hospitalized patients with Covid-19 — preliminary report, N. Engl. J. Med. (2020), https://doi.org/10.1056/nejmoa2022146.

[7] L. Venkateswaran, F. Scaglia, V. McLin, P. Hertel, O.A. Shchelochkov, S. Karpen, D. Mahoney, D.L. Yee, Ornithine transcarbamylase deficiency: a possible risk factor for thrombosis, Pediatr. Blood Cancer 53 (2009) 100–102, https://doi.org/10.1002/pbc.22016.

[8] G. Avruscio, G. Camporese, E. Campello, E. Bernardi, P. Persona, C. Passarella, F. Noventa, M. Cola, P. Navalesi, A. Cattelan, I. Tiberio, A. Boscolo, L. Spiezia, P. Simioni, COVID-19 and venous thromboembolism in intensive care or medical ward, Clin. Transl. Sci. (2020), https://doi.org/10.1111/cts.12907.

[9] A.S. Galanopoulou, V. Feratrassou, D.J. Correa, K. Cherian, S. Dubertstein, J. Gursky, R. Hanumanthu, C. Hung, I. Molineo, O. Khodakivska, A.D. Legatt, P. Patel, J. Rosengard, E. Rubens, W. Sugrue, E. Yozawitz, M.F. Mehler, K. Ballaban-Gil, S.R. Haut, S.L. Moshe, A. Boro, EEG findings in acutely ill patients investigated for SARS-CoV-2/COVID-19: a small case series preliminary report, Epilepsia Open. 5 (2020) 314–324, https://doi.org/10.1002/epio.12399.

[10] G. Assenza, J. Lanzone, F. Brigo, A. Coppola, G. Di Gennaro, V. Di Lazzaro, L. Ricci, A. Romigi, M. Tombini, O. Mecarelli, Epilepsy Care in the Time of COVID-19 pandemic in Italy: risk factors for seizure worsening, Front. Neurol. 11 (2020) 737, https://doi.org/10.3389/fneur.2020.00737.

[11] D. Vohora, S. Jain, M. Tripathi, H. Potschka, COVID-19 and seizures: is there a link? Epilepsia. 61 (2020) 1840–1853, https://doi.org/10.1111/epi.16656.

[12] J. Lanzone, C. Cenci, M. Tombini, L. Ricci, T. Tuto, M. Piccioli, A. Marrelli, O. Mecarelli, G. Assenza, Glimpsing the impact of COVID19 lock-down on people with epilepsy: a text mining approach, Front. Neurol. 11 (2020) 870, https://doi.org/10.3389/fneur.2020.00870.

[13] M. Tombini, G. Assenza, L. Quintiliani, L. Ricci, J. Lanzone, R. De Moja, M. Ulivi, V. Di Lazzaro, Epilepsy-associated stigma from the perspective of people with epilepsy and the community in Italy, Epilepsy Behav. 98 (2019) 66–72, https://doi.org/10.1016/j.yebeh.2019.06.026.

[14] M. Tombini, G. Assenza, L. Quintiliani, L. Ricci, J. Lanzone, M. Ulivi, V. Di Lazzaro, Depressive symptoms and difficulties in emotion regulation in adult patients with epilepsy: association with quality of life and stigma, Epilepsy Behav. 107 (2020), https://doi.org/10.1016/j.yebeh.2020.107073.