Case Report

Metabolic stroke-like episode in a child with FARS2 mutation and SARS-CoV-2 positive cerebrospinal fluid

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1. Introduction

Mutations in the FARS2 gene yield a set of mitochondrial disorders associated with dysfunctional mitochondrial phenylanyl-tRNA synthetase 2 [1]. The clinical phenotypes are variable, ranging from infantile-onset epileptic mitochondrial encephalopathy to later-onset spastic paraplegia [2]. The epileptic phenotype is the more severe of the two, with developmental delay, seizure onset within the first year of life, and death in early childhood frequently reported in the literature [1]. Although a mitochondrial disorder, mutations in the FARS2 gene have not been reported to be associated with metabolic stroke-like episodes, as observed in other mitochondrial disorders such as Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke Like Episodes (MELAS) [1,2].

There have been multiple reports of neurologic manifestations associated with the novel coronavirus (SARS-CoV-2) although children seem to have infrequent complications [3,4]. In persons with neurologic complications of SARS-CoV-2, it appears that the inflammatory cascade, as opposed to the virus itself, is causative for the pathology observed, particularly in cerebrovascular accidents [5–8].

Here the authors report a novel case of metabolic stroke-like episodes in a child with FARS2 gene- associated combined oxidative phosphorylation deficiency type 14 with spastic-paraparesis following infection with SARS-CoV-2 with both active serum and CSF PCR positivity.

2. Case report

An 11-year-old male with history of FARS2-related combined oxidative phosphorylation deficiency type 14, spastic paraparesis, and mild developmental delay presented with increased work of breathing, poor oxygen saturation, and lactic acidosis (peak 85.3 mg/dL). He was noted to be SARS-CoV-2 PCR positive on nasopharyngeal swab. His pulmonary distress coincided with acute changes to his neurologic status. On examination, he displayed a new onset gaze preference towards the left, along with opsoclonic eye movements and global aphasia. Pertinent laboratory values are displayed in Table 1. Urgent neuro-imaging revealed discrete areas of restricted diffusion in the periaqueductal gray matter and dorsal midbrain as well as the bilateral red nuclei (Fig. 1). Given concern for active infection associated metabolic stroke, a lumbar puncture was performed (Table 1). Notably, the patient had no pleocytosis, although had elevated lactic acid and a positive SARS-CoV-2 PCR in the CSF.

The ketogenic diet was initiated to correct his metabolic acidosis, with subsequent normalization of his venous blood gas and lactic acid. His hospitalization was complicated by development of a rubral tremor and signs of autonomic dysfunction, including fluctuations in temperature, heart rate, blood pressure, GI motility and hyperhidrosis. Low dose propranolol was trialed, with stabilization of his heart rate and temperature. On discharge, the patient continued to be globally aphasic and have mild but present opsoclonic eye movements.
SARS-CoV-2 infection is still unclear if the neuro-pathology associated with infection or the inflammatory cascade associated with infection was causative or not. Interestingly, even amongst patients with mitochondrial disorders prone to metabolic stroke-like episodes, there have been no reported cases associated with SARS-CoV-2 to this point. While of great interest in its two novel findings, this case has limitations. This case reports a rare case of SARS-CoV-2 associated metabolic stroke-like episode in a child with FARS2 deficiency. This case is novel for two primary reasons. Firstly, this is the first report of a metabolic stroke-like episode in a child with FARS2 deficiency. Secondly, the presence of lactic acidosis and CSF positivity for SARS-CoV-2 could be explained in this manner, with the acidotic milieu triggering cytolyphagia and cell death, seen as restricted diffusion on neuroimaging. The predilection for the dorsal midbrain, while symmetric in a pattern characteristic of mitochondrial disorders, is of unclear significance.

An unanswered question in this case is why a patient with FARS2 gene mutation would be susceptible to metabolic stroke-like episode when this has never been reported in the literature. If the patient’s genetic defect is not associated with metabolic stroke-like episodes, making it possible that SARS-CoV-2 infection may have caused metabolic failure itself [14].

3. Discussion

The authors report a novel case of SARS-CoV-2 associated metabolic stroke-like episode in a child with FARS2 deficiency. This case is novel for two primary reasons. Firstly, this is the first report of a metabolic stroke-like episode in any child with primary SARS-CoV-2 infection. Although this patient would be considered susceptible due to his mitochondrial gene mutation, FARS2 deficiency (any phenotypic presentation) is not classically associated with metabolic stroke. In this case, the positive CSF PCR for SARS-CoV-2 raises the question of whether active infection or the inflammatory cascade associated with infection was causative or not.

There has been only one documented case of SARS COV2 detected in the CSF of a pediatric patient, a 10-week-old with suspected sepsis [9–12]. Several cases have shown pleocytosis and elevated protein but have failed to detect the virus within the CSF, indicating rapid CSF viral clearance [4,14]. Rather, most pediatric studies have demonstrated abnormalities of serum inflammatory markers, including D-dimer, procalcitonin, creatine kinases, and interleukin-6 [11,13]. As hypothesized in adult studies, it is unclear if the neuro-pathology associated with SARS-CoV-2 is infection triggered or of a post-infectious inflammatory nature as these laboratory disturbances would indicate [5,6,8,9]. Here, the capture of the virus in the CSF indicates the possibility that the actual

Table 1

| Serum lab                | Value       | Reference value |
|-------------------------|-------------|-----------------|
| WBC                     | 12.07 K/ul  | 4.31–11         |
| HGB                     | 9.5 g/dl    | 10.8–13.4       |
| HCT                     | 28.5%       | 32.2–39.8       |
| PLTE                    | 342 K/ul    | 342–369         |
| Sodium                  | 140 mEq/L   | 135–145         |
| Potassium               | 4.6 mEq/L   | 3.6–5           |
| Chloride                | 108 mEq/L   | 98–107          |
| CO2 total               | 18 mEq/L    | 22–30           |
| Creatinine              | 0.90 mg/dl  | 0.7–1.5         |
| Glucose level           | 121 mg/dl   | 60–115          |
| Lactic Acid             | 537–853.3 mg/dl | 6.3–18.9 |

Chloride

| CSF Lab                  | Value       | Reference value |
|--------------------------|-------------|-----------------|
| RBC                      | 221 Cell/mm3| 0–5             |
| WBC                      | 2 Cell/mm3  | 0–4             |
| Glucose                  | 52 mg/dl    | 37–75           |
| Protein                  | 31 mg/dl    | 12–60           |
| Lactate                  | 30.6 mg/dl  | 0–20            |
| Pyruvate                 | 0.75 mg/dl  | 0.50–1.70       |
| Amino Acid CSF           |             |                 |
| Citrulline 6.1 uMOL/L    | 1–5         |                 |
| Alanine 47.5 uMOL/L      | 10–34       |                 |
| Isoleucine 9.5 uMOL/L    | 2–6         |                 |
| Leucine 21.8 uMOL/L      | 8–18        |                 |
| Paraneoplastic Panel     | Negative    | Negative        |
| Film Array Meningitis/Encephalitis Panel | Negative | Negative |
| SARS-CoV-2 PCR           | Positive    | Negative        |

Bold indicates the Abnormal values.

* In house PCR film array tests for Escherichia coli K1, Haemophilus influenza, Listeria monocytogenes, Neisseria meningitidis (encaps), Streptococcus agalactiae, Streptococcus pneumoniae, Cytomegalovirus, Enterovirus, Herpes simplex virus 1, 2, 6, Human parechovirus, Varicella Zoster Virus, Cryptococcus neoformans/ gattii.

SARS-CoV-2 virus could have potentially triggered the metabolic failure observed in this patient. This is of particular interest in that this patient’s genetic defect is not associated with metabolic stroke-like episodes, making it possible that SARS-CoV-2 infection may have caused metabolic failure itself [14].

An unanswered question in this case is why a patient with FARS2 gene mutation would be susceptible to metabolic stroke-like episode when this has never been reported in the literature. If the patient’s genetic defect is not associated with metabolic stroke-like episodes, making it possible that SARS-CoV-2 infection may have caused metabolic failure itself [14].

Fig. 1. Axial image DWI images demonstrating restricted diffusion in the periaqueductal grey matter and dorsal midbrain.
Conflict of interest disclosures

The authors have no conflicts of interest to disclose.

Funding/support

No funding was secured for this study.

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