Molecular Genetics and Metabolism Reports 27 (2021) 100756

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Case Report

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

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ARTICLE INFO

Keywords:
FARS2
Mitochondrial
Stroke
SARS-CoV-2
Pediatric
Cerebrospinal fluid

ABSTRACT

The novel SARS-CoV-2 has infected over 48 million persons around the world. Children have been spared with regards to symptoms and sequelae of this highly infectious virus and in those with neurologic issues, the virus has not been present in the cerebrospinal fluid. Here, the authors present the first case of metabolic stroke-like episode with SARS-CoV-2 present in the cerebrospinal fluid in a child with a FARS2 deficiency. This report suggests a possible association of SARS-COV-2 infection and metabolic stroke-like episode, even in the absence of a phenotype classically associated with metabolic stroke-like episodes.

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 neuroimaging 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.

Abbreviations: PCR, (polymerase chain reaction).

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https://doi.org/10.1016/j.ymgmr.2021.100756
Received 4 April 2021; Accepted 5 April 2021
Available online 14 April 2021

Table 1
Serum lab findings on admission and lumbar puncture results.

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	0.7–1.50
Glucose level	**121** mg/dL	60–115
Lactic Acid	Range: **33.7–85.3 mg/dL** Mean 50.72 mg/dL	6.3–18.9
AST	39 units/L	15–46
ALT	43 units/L	(<44
CK	66 units/L	57–374
Alk phos	146 units/L	60–280
PT	12.1 s (	8.8–12.5
PT-INR	1.1	(>4
PTT	25 s	25–39
D-Dimer	525 ng/mL	(>570
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 Alanine **47.5** uMOL/L Isoleucine C **9.5** uMOL/L Leucine **21.8** uMOL/L	1–5 10–34 2–6 8–18
Paraneoplastic Panel	Negative	Negative
Film Array Meningitis/Encephalitis Panel[a]	Negative	Negative
SARS-COV-2 PCR	**Positive**	**Negative**

Bold indicates the Abnormal values.

[a] In house PCR film array tests for *Escherichia coli* K1, Haemophilius 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.

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

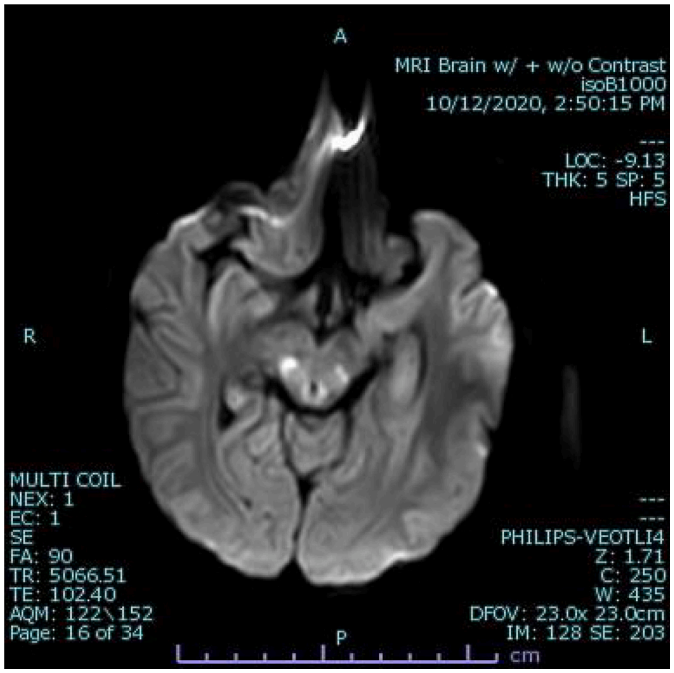

Fig. 1. Axial image DWI images demonstrating restricted diffusion in the periaqueductal grey matter and dorsal midbrain.

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. In this case, the patient's hyperlactacidemia was indicative of a severe metabolic crisis, which although infrequently reported in persons with FARS2 gene mutations, is known. It is possible that this systemic metabolic failure caused by the direct infection with SARS-CoV-2 may have increased blood-brain barrier permeability, allowing the virus privileged entry into the central nervous system. In this case, it could be surmised that the presence of lactic acidosis and CSF positivity for SARS-CoV-2 could best be explained in this manner, with the acidotic milieu triggering cytopathy 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.

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 gene mutation which is not generalizable to other individuals with mitochondrial disorders. While these disorders are rare, rates of infection with SARS-CoV-2 across the world have been high. It is possible that there are no reports because persons with mitochondrial or metabolic disorders may be more likely to socially distance than other age-adjusted neurotypical individuals. Although CSF positivity for SARS-CoV-2 was detected, determining if the virus or the inflammatory cascade is responsible for the acute neurologic deterioration incurred is impossible although very suspicious for the former.

This case raises the concerns for SARS-CoV-2 associated metabolic stroke-like episodes in susceptible individuals. Social distancing, mask-wearing, and infectious precautions are critical for at-risk individuals with genetic, metabolic, and mitochondrial disorders.

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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