Hormone Research in Paediatrics

Novel Insights from Clinical Practice / Case Report

Horm Res Paediatr
DOI: 10.1159/000525227

Received: February 20, 2022
Accepted: April 28, 2022
Published online: May 24, 2022

New-Onset Primary Adrenal Insufficiency and Autoimmune Hypothyroidism in a Pediatric Patient Presenting with MIS-C

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Established Facts

- Emerging evidence suggests SARS-CoV-2 is a potential trigger for autoimmune conditions.
- Primary autoimmune adrenal insufficiency and autoimmune thyroiditis have been previously reported in adult patients with COVID-19.

Novel Insights

- This is the first report of autoimmune primary adrenal insufficiency and hypothyroidism (autoimmune polyglandular syndrome type 2) in a pediatric patient diagnosed with COVID-19.
- SARS-CoV-2 infection may trigger the clinical manifestation of autoimmune endocrinopathy in susceptible children.

Keywords
Adrenal insufficiency · COVID-19 · Hypothyroidism · Adolescent

Abstract

Introduction: There is emerging speculation that the inflammatory state associated with SARS-CoV-2 infection may trigger autoimmune conditions, but no causal link is established. There are reports of autoimmune thyroiditis and adrenal insufficiency in adults post-COVID-19. We describe the first pediatric report of adrenal insufficiency and autoimmune hypothyroidism after COVID-19. ***Case Presentation:*** A 14-year-old previously healthy girl, with vitiligo, presented in shock following 1 week of fever, lethargy, diarrhea, and vomiting. Three weeks prior, she had congestion and fatigue and known familial exposure for COVID-19. Labs were remarkable for sodium 129 mmol/L, K 4.3 mmol/L, creatinine 2.9 mg/dL, hemoglobin 8.3 g/dL, and positive COVID-19 PCR and SARS-CoV-2 IgG. She was resuscitated with normal saline and required pressor support. EKG showed abnormal repolarization presumed secondary to myocarditis. She met the criteria for multisystem inflammatory syndrome in children (MIS-C), received intravenous immune globulin and IL-1R antagonist and was admitted for intensive care. Persistent hypotension despite improved inflammatory markers

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and undetectable cortisol led to initiation of hydrocortisone. She was then able to rapidly wean off pressors and hydrocortisone within 48 h. Thereafter, tests undertaken for persistent bradycardia confirmed autoimmune hypothyroidism with TSH 131 μU/mL, free T4 0.85 ng/dL, and positive thyroid autoantibodies. Basal and stimulated cortisol were <1 μg/dL on a standard 250 μg cosyntropin stimulation test, with baseline ACTH >1,250 pg/mL confirming primary adrenal insufficiency. Treatment was initiated with hydrocortisone, levothyroxine, and fludrocortisone. Adrenal sonogram did not reveal any hemorrhage and anti-adrenal antibody titers were positive. The family retrospectively reported oligomenorrhea, increased salt craving in the months prior, and a family history of autoimmune thyroiditis. The cytokine panel was notably different from other cases of MIS-C. ***Conclusion:*** This is the first pediatric report, to our knowledge, of primary adrenal insufficiency and hypothyroidism following COVID-19, leading to a unique presentation of autoimmune polyglandular syndrome type 2. The initial presentation was attributed to MIS-C, but the subsequent clinical course suggests the possibility of adrenal crisis. It remains unknown if COVID-19 had a causal relationship in triggering the autoimmune adrenal insufficiency and hypothyroidism.

Introduction

Viral infections have been proposed as environmental triggers for several autoimmune conditions in genetically susceptible individuals [1]. There is emerging evidence that COVID-19 caused by SARS-CoV-2 is also associated with several autoimmune conditions during the infection onset or the recovery phase such as autoimmune hemolytic anemia, vasculitis, arthritis, demyelinating disorders, and immune thrombocytopenic purpura with a growing number of reports of conditions involving diverse organs and systems [2]. Multisystem inflammatory syndrome in children (MIS-C) is a rare but severe systemic autoinflammatory condition described in children characterized by fever, multi-organ involvement, and elevated inflammatory markers in the context of recent COVID-19 infection [3]. The pathogenetic mechanisms of both autoinflammatory and autoimmune diseases associated with COVID-19 infection are as yet poorly understood but may involve molecular mimicry, bystander activation, and loss of immune tolerance [4]. Autoimmune endocrine conditions described following SARS-CoV-2 include type 1 diabetes [5], autoimmune thyroiditis including hypothyroidism, Graves' disease [6], and one case of autoimmune adrenalitis in an adult [7]. We report the first case of autoimmune polyglandular syndrome 2 (APS2) characterized by new-onset primary adrenal insufficiency and autoimmune primary hypothyroidism diagnosed in an adolescent, in the context of COVID-19 infection, presenting with severe systemic symptoms suggestive of MIS-C.

Table 1. Initial laboratory results

Test name	Result	Reference range	Units
Sodium	129	135–146	mmol/L
Potassium	4.3	3.5–5.2	mmol/L
Bicarbonate	20	18–32	mmol/L
Glucose	70	65–140	mg/dL
BUN	33	5–25	mg/dL
Creatinine	2.9	0.4–1.2	mg/dL
Hemoglobin	8.3	12–15.5	g/dL
C-reactive protein	8.13	0–1	mg/dL
ESR	105	0–20	mm/h
CK	796	20–253	U/L
CK-MB	3	≤5	ng/mL
Troponin	14	<54	ng/L
BNP	5.9	0–100	pg/mL
IL 2 receptor, soluble	1,180.3	266.5–1,410.4	pg/mL
IL 6	13.1	≤2.5	pg/mL
IL 10	19.7	≤5.3	pg/mL

BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate; CK, creatine kinase; MB, myocardial band; IL, interleukin; BNP, brain natriuretic peptide; CK-MB, creatine kinase myocardial band.

Case Presentation

A 14-year-old female, previously healthy, with a history of vitiligo diagnosed at age 9 years, presented with symptoms of fever up to 104 F, lethargy, diarrhea, and vomiting for 1 week. Three weeks prior, she had a history of congestion and fatigue and had tested negative for SARS-CoV-2. She had household exposure to the virus, and her SARS-CoV-2 PCR and IgG antibodies were positive on the day of admission. Her labs were notable for hyponatremia to 129 mmol/L, creatinine 2.9 mg/dL, hemoglobin 8.3 g/dL, with elevated C-reactive protein, and sedimentation rate, while her cardiac inflammatory markers creatine kinase myocardial band, troponin, and B-type natriuretic peptide (BNP) were initially normal (Table 1). Her EKG was notable for right bundle branch block, prolonged QT, and junctional rhythm. Her echocardiogram did not show pericardial effusion and she had good left ventricular function. Recognized to have hypotensive shock, she was resuscitated with normal saline, initiated on an epinephrine drip, and admitted to the intensive care unit.

Given the history of fever, gastrointestinal and cardiac involvement, elevated inflammatory markers and positive COVID-19 an-

tibodies and PCR, and no alternate diagnosis at the time, she met the criteria for the diagnosis of MIS-C. A cytokine panel was sent; the results are summarized in Table 1. She was started on empiric antibiotic treatment, as well as intravenous immune globulin, and interleukin-1 receptor antagonist (Anakinra). She also received a blood transfusion for worsening anemia (Hemoglobin 6.9 g/dL). During the admission, she developed nonsustained ventricular tachycardia, attributed to possible myocarditis, requiring lidocaine infusion, and was then switched to an oral anti-arrhythmic medication, mexiletine. She initially improved and was weaned off the epinephrine drip, but 3 days later, she developed hypothermia and hypotension and was restarted on vasopressors and empiric antibiotic treatment. Due to persistent hemodynamic instability and catecholamine dependence, despite improvement in her inflammatory markers, a random cortisol was drawn and was <1 μg/dL. Hydrocortisone stress dose at 50 mg/m^2/day was initiated, and this led to improvement in her clinical condition and was able to wean off vasopressor support.

The following day, the development of unexplained bradycardia, while on oral antiarrhymics, prompted investigation with thyroid function tests. She was found to be hypothyroid, with TSH elevated to 131.18 μU/mL (normal range 0.52–4.13 μU/mL), low free T4 0.85 ng/dL (normal range 1.1–1.6 ng/dL), elevated thyroid peroxidase antibody 5,744 IU/mL (normal range <35 IU/mL), and thyroglobulin antibody 238.0 IU/mL (normal range <20 IU/mL) titers, and levothyroxine 1.4 mg/kg was initiated. Of note, at this time, the parents provided a further history that she had experienced some symptoms of fatigue, constipation, dry skin, oligomenorrhea, and cold intolerance, and a family history of autoimmune hypothyroidism in her grandmothers. She had menarche when she was 13 years old and had been having regular periods every 3 weeks until 4 months prior to the presentation to the hospital. During this time, she did not have any menses and had some spotting again during the hospitalization. Following the diagnosis of autoimmune hypothyroidism, hydrocortisone was discontinued and a standard-dose ACTH stimulation test was completed with baseline ACTH level drawn as part of the institutional protocol. Baseline ACTH level was elevated to >1,250 pg/mL (normal range 9–57 pg/mL), and both baseline and stimulated cortisol were <1 μg/dL, confirming a diagnosis of primary adrenal insufficiency. She was restarted on hydrocortisone 50 mg/m^2/day and weaned down to a maintenance physiologic dose. Her 21-hydroxylase anti-adrenal antibodies were positive, while the adrenal sonogram did not identify any evidence of hemorrhage or infarction. Aldosterone was <1 ng/dL and plasma renin was 0.43 ng/mL/h (normal range 0.25–5.82), and she was started on fludrocortisone 0.05 mg daily. After discharge, we elicited a history of salt craving for a couple of months from other family members. There was no evidence of mucosal or skin hyperpigmentation either by physical exam or per the history that would be suggestive of chronic ACTH elevation. Of note, she is non-Hispanic white and we did not think race/ethnicity may have affected the recognition of skin and mucosal hyperpigmentation either. With confirmed APS2, she is followed in the endocrine clinic and being monitored for other autoimmune conditions with negative screening tests for celiac disease, pernicious anemia, and hypoparathyroidism. Although she does not have any clinical or laboratory evidence of hyperglycemia, the presence of glutamic acid decarboxylase (GAD65) antibodies (33 IU/mL, normal range <5 IU/mL) is consistent with APS2 and suggests increased predisposition for type 1 diabetes. A review of growth records revealed no significant weight loss prior to the presentation and normal growth velocity for age in the previous years. A few weeks after discharge, she developed diffuse hair loss, which was thought to be multifactorial secondary to possible alopecia aerata, telogen effluvium, and hypothyroidism. It has since resolved without treatment. At the 2-month follow-up, she reported having menstruation twice, spaced 3 weeks apart. FSH was initially elevated to 14.93 mIU/mL but normalized in follow-up evaluation, but she will remain under surveillance for increased risk of primary ovarian insufficiency.

Discussion

This young, previously healthy adolescent patient, with vitiligo, was hospitalized for hypotensive shock, following COVID-19 infection, initially treated as MIS-C and was found to have autoimmune thyroiditis and primary adrenal insufficiency. The constellation of autoimmune conditions is consistent with a diagnosis of APS2. APS2 has an incidence of 1 in 20,000 and is rare in children [8]. This is the first pediatric case report of APS2 diagnosed after a recent COVID-19 infection.

Adrenal crisis and shock secondary to new-onset primary adrenal insufficiency can occur in children [9]. Her initial presentation, with multisystem involvement, fever, elevated inflammatory markers, and presence of SARS-CoV-2 exposure was consistent with a diagnosis of MIS-C [10]. However, the diagnosis of MIS-C is a diagnosis of exclusion, and it is plausible that her symptoms may all be attributable to unrecognized adrenal insufficiency and hypothyroidism [10]. Her dependence on vasopressors raised suspicion for adrenal insufficiency and persistent bradycardia prompted thyroid screening. Critical illness-related corticosteroid insufficiency can present in 30% of critically ill children [11] and is indistinguishable from primary adrenal insufficiency during the initial period but is often reversible [12]. The presence of vitiligo and confirmation of autoimmune hypothyroidism led us to suspect and then confirm primary adrenal insufficiency. Though she had significant cardiac involvement, which was initially attributed to possible inflammation of the myocardium due to MIS-C, cardiac inflammatory markers were not significantly elevated at initial presentation, and symptoms persisted even after they normalized. Her EKG findings could also be explained by adrenal insufficiency, and concomitant hypothyroidism which has been reported to cause sinus bradycardia slowed AV nodal conduction, low QRS voltages, and disorders of ventricular repolarization (T wave inversion, QT prolongation) in

the absence of potassium abnormalities [13–15]. Notably, her inflammatory panel was different from typical MIS-C cases [16]. Her interleukin and inflammatory marker levels were normal or only slightly elevated, whereas in the acute phase of MIS-C, very high levels of cytokines are observed, particularly interleukin-6, interleukin-10, soluble interleukin-2 receptor, and tumor necrosis factor [16, 17]. Additionally, troponin, B-type natriuretic peptide, and N-terminal pro-B-type natriuretic peptide were initially normal and peak N-terminal pro-B-type natriuretic peptide was considerably lower than what is described in the MIS-C literature [18].

Primary autoimmune adrenal insufficiency has been recently reported in one adult patient with COVID-19. Sánchez et al. [7] describe a case of a 65-year-old woman with type 2 diabetes and hypothyroidism, who developed autoimmune adrenal insufficiency 5 months after asymptomatic COVID-19 infection. The diagnosis was confirmed with an elevated ACTH level to 1,944 pg/mL, poor cortisol response to high dose cosyntropin test, and positive 21-hydroxylase adrenal autoantibodies. There is mounting evidence of the effect of SARS-CoV-2 on the adrenal glands in previously healthy patients, causing various degrees of primary and central adrenal insufficiency [19]. Possible mechanisms include the direct invasion of the virus into the adrenal gland, as evidenced by postmortem studies, or the binding of the virus to angiotensin-converting enzyme II (ACE2) receptors present in adrenocortical cells [20, 21]. Other causes of primary adrenal insufficiency associated with COVID-19 infection have been described, including bilateral adrenal hemorrhage [22, 23] and infarction [24–26]. The majority of those cases are reported in adults, with the exception of a neonatal case, a full-term baby boy born to a mother with severe COVID-19, who developed bilateral adrenal hemorrhage on the 7th day of life [23].

COVID-19 is emerging as a potential trigger for autoimmune conditions, even in patients with no predisposition [27]. A hyperinflammatory state precipitated by SARS-CoV-2 has been hypothesized to lead to immunological dysregulation and autoimmune reactions [28]. Several cases of autoimmune thyroiditis have already been reported [6]. Our patient was experiencing symptoms consistent with hypothyroidism and adrenal insufficiency, including constipation, oligomenorrhea, fatigue, and salt craving prior to her presentation; however, she showed notable clinical deterioration following the COVID-19 infection. Interestingly, she did not have hyperpigmentation, which would be expected with long-standing elevation in ACTH, or the clinical findings of severe long-standing hypothyroidism. The role of COVID-19 in the etiopathogenesis of APS2 in this case remains unclear, but we suspect that it may have contributed to the rapid progression and severe clinical manifestations of both adrenal insufficiency and hypothyroidism leading to the presentation akin to MIS-C.

Conclusion

We report a rare case of a pediatric patient with new diagnosis of APS2 shortly after SARS-CoV-2 infection. New-onset hypothyroidism and primary adrenal insufficiency led to a severe clinical presentation resembling MIS-C. In susceptible patients, including those with a history of autoimmune conditions, clinical surveillance for manifestations of other autoimmune conditions potentially triggered by COVID-19 may be prudent.

Statement of Ethics

On June 1, 2022, this case was acknowledged by the Children's National Hospital Institutional Review Board (IRB) as meeting criteria for a case report or case series. According to institutional policy, the project was deemed exempt from full review. Written informed consent was obtained from the participant's parent for publication of the details of their medical case.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding sources to declare.

Author Contributions

Dr. Myrto Eleni Flokas participated in data collection and interpretation, prepared tables and figures, wrote and drafted the initial manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Dr. Victoria H. Bustamante participated in data interpretation, wrote and drafted the initial manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Dr. Roopa Kanakatti Shankar participated in data collection and interpreta-

tion, wrote and drafted the initial manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this published article. Further inquiries can be directed to the corresponding author.

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