Post-infectious inflammatory syndrome associated with SARS-CoV-2 in a paediatric patient with Down syndrome

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SUMMARY

Neurological complications of SARS-CoV-2 continue to be recognised. In children, neurological phenomenon has been reported generally in the acute infectious period. It is possible that SARS-CoV-2 could trigger an immune-mediated post-infectious phenomenon. Here, we present a unique case of post-infectious marantic cardiac lesion causing cerebrovascular accident in a patient with Down syndrome.

BACKGROUND

Down syndrome (DS) is a well-described genetic disorder typically associated with trisomy of chromosome 21, with a prevalence of 1 in 600 live births in the USA.[1] Persons with DS are known to have immune dysregulation, which most frequently manifests as increased risk of infections and inadequate vaccine responses.[1 2] Although there are emerging data on the impact of primary infection with SARS-CoV-2 in this population,[3] no reports of post-infectious phenomenon, nor cerebrovascular disease, have been reported in children with DS.

SARS-CoV-2 has been reported in the USA for over 7 months, yet limited data have emerged on late post-infectious phenomenon in children. Multisystem inflammatory syndrome in children (MIS-C) has emerged as a recognised concept regarding the early post-infectious ramifications of SARS-CoV-2 infection in paediatric patients, producing a more severe Kawasaki syndrome-like presentation.[4] This literature has not identified neurological sequelae from MIS-C, matching early data out of China indicating low rates of neurological complications.[4]

The role of SARS-CoV-2 in the early activation of the inflammatory cascade has provided a construct to evaluate cerebrovascular disease in adults.[5 6] There are reports regarding primary SARS-CoV-2 infection producing hypercoagulable states and cerebrovascular accidents (CVAs) in otherwise healthy adults with an estimated risk of 0.5%, although the exact aetiology remains unclear and likely heterogeneous.[5 6] Here, we report the first case of potential SARS-CoV-2-related CVA in a paediatric patient and the first description of a post-infectious inflammatory cardiac lesion in a child.

CASE PRESENTATION

A 3-year-old girl with Down syndrome (DS), unbalanced atrioventricular (AV) canal status post a 1.5 ventricle repair, a Glenn shunt, atrial septal defect (ASD)/ventricular septal defect (VSD) patch, veno-venous collateral ligation resulting in four-chamber physiology with hypoplastic right ventricle, pulmonary hypertension and obstructive sleep apnoea with a recent primary infection with SARS-CoV-2 3 months prior presented to the hospital with recurrent fever of unknown origin. In her initial visit to the emergency department, she underwent a broad infectious workup which was negative, including SARS-CoV-2 nasopharyngeal PCR, but had presence of SARS-CoV-2 immunoglobulin G (IgG) antibodies (titre: 6.1, reference range <0.7). She was subsequently discharged because of improved oral intake and no identifiable pathology to warrant admission; however, she returned the following week with new onset dysarthria, with wide-spaced gait and falling.

Her examination was remarkable for wide-based gait, irritability, dysarthria and diminished expressive language. She had no other localising findings including nystagmus, dysmetria or titubation while sitting. She subsequently developed rigours associated with hyperthermia and with significant and persistent episodes of desaturations and cyanosis. Notably, the patient's fevers were responsive to antipyretic interventions, improving her irritability, rigours and frequency of desaturations with administration. Given high antibody titres in the setting of concern for cardiac dysfunction, a presumptive diagnosis of multisystem inflammatory syndrome in children (MIS-C) was made even though SARS-CoV-2 PCR was negative. The patient continued to have tachycardia with wide heart rate variability and pulse pressures, but had few other overt features of MIS-C.

INVESTIGATIONS

Serum and cerebrospinal fluid (CSF) findings are reported in table 1 but were notable for pancytopenia and elevated inflammatory biomarkers. Once clinically stable, neuroimaging was obtained with an MRI of the brain which was remarkable for multiple areas of embolic infarct without surrounding oedema in addition to an area of haemorrhage within the left cerebellar hemisphere (figure 1). There was low suspicion that these were septic emboli given lack of inflammatory changes around the areas of infarct, which primarily seeded the grey/white junctions. This prompted a cardiac investigation with an echocardiogram

Table 1 Clinical data

Laboratory test	Patient	Reference value
Serum		
TSH	2.07 ng/dL	0.5–5.0 ng/dL
Free T4	1.63 ng/dL	09.6–1.72 ng/dL
CRP (max)	15.5 mg/dL	0.0–0.9 mg/dL
ESR (max)	20 mm/hour	1–10 mm/hour
Compliment C3	104 mg/dL	80–178 mg/dL
Compliment C4	16 mg/dL	13–47 mg/dL
Antinuclear antibody	Negative	Negative
DNase-B antibody 151 U/L negative		
Proteinase 3 antibody	0.2	<0.4
Myeloperoxidase antibody	<0.2	<0.4
Cardiolipin IgA	22 U/L	<13.9 U/L
Cardiolipin IgG	70 U/L	<9.9 U/L
Cardiolipin IgM	1.5 U/L	<9.9 U/L
Toxoplasma IgM/IgG	Negative	Negative
Rickettsia IgM/IgG	Negative	Negative
QuantiFERON	Negative	Negative
Brucellosis IgM/IgG	Negative	Negative
Legionella IgA/IgG	Negative	Negative
Q Fever IgM/IgG Phase 1/2 negative negative		
Cerebrospinal fluid		
WCC	31 cells/mm^3	<5 cells/mm^3
RCC	28 000 cells/mm^3	0 cell/mm^3
% lymphocytes	9%	30%–90%
Glucose	38 mg/dL	37–75 mg/dL
Protein	110 mg/dL	15–60 mg/dL
Oligoclonal bands	Negative	Negative
IgG index	1.15	<0.60
Neopterin	93 nmol/L	7–65 nmol/L
Infectious PCR panel	Negative	Negative
Culture negative negative		
Gram stain	Negative	Negative
Paraneoplastic/encephalitis panel (Mayo)	Negative	Negative

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; TSH, thyroid stimulating hormone.

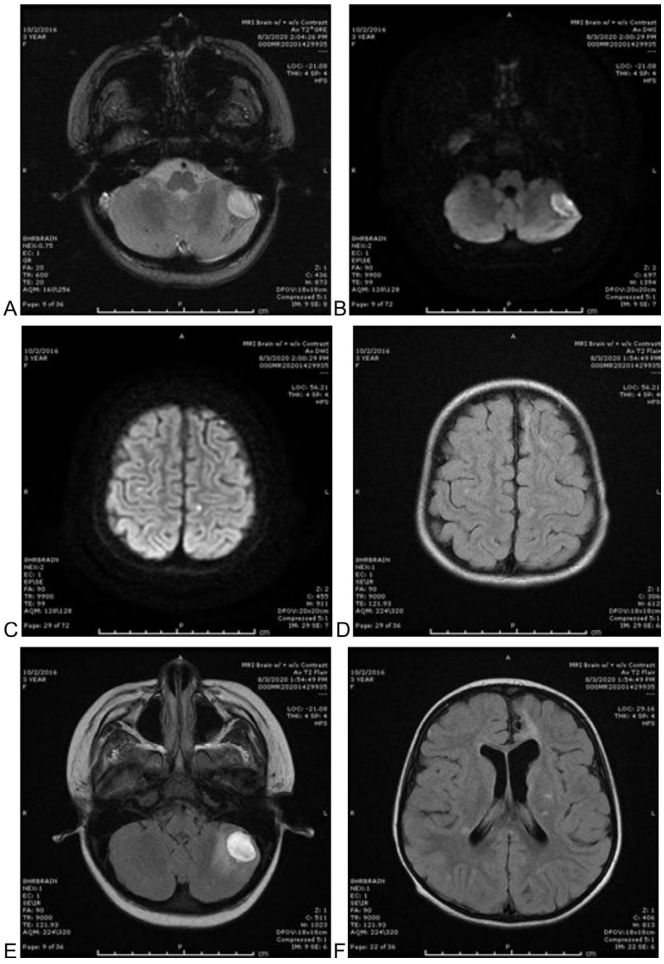

Figure 1 Neuroimaging findings. (A) Axial GRE sequence demonstrating left cerebellar hemisphere haemorrhagic conversion. (B) Axial DWI sequence demonstrating restricted diffusion in the left cerebellum consistent with cerebrovascular accident (CVA). (C) Axial T2 FLAIR sequence demonstrating signal prolongation in multiple anterior vascular distributions. (D) Axial DWI sequence demonstrating restricted diffusion in distal cortical areas consistent with embolic stroke. (E) Axial T2 FLAIR sequence demonstrating signal prolongation along cerebellar infarction. (F) Axial T2 FLAIR sequence demonstrating signal prolongation along the periventricular zones. Of note, there is limited oedema surrounding the areas of thromboembolic infarct, aside from the left cerebellar hemisphere, likely due to evidence of haemorrhagic conversion and subsequent vasogenic oedema. DWI, diffusion weighted imaging; FLAIR, fluid-attenuated inversion recovery; GRE, gradient rechalled echo.

demonstrating a large thrombus identified along the length of her ASD patch, extending across the plane of the AV valve and along the VSD patch with protrusions into the ventricle via the mitral valve. She had an echocardiogram obtained 2 months prior as an outpatient that was noted to be stable.

TREATMENT

As the patient's prior cardiac surgeries were deemed high risk for the sedation for an MRI, she was administered empiric intravenous immunoglobulin (IVIg) of 2 g/kg over 2 days and 3 days of intravenous methylprednisolone (30 mg/kg/day). She was also on empiric ceftriaxone, but after 48 hours of culture negative status, this was discontinued. The patient had improvement of her mental status, mood and balance within 5 days of completion of IVIg. Additionally, she engaged more with providers, spoke more, although with notable dysarthria, and had more symmetric movement of her extremities with generally improved truncal stability. Further, her C-reactive protein (CRP) was downtrending, which is further detailed in figure 2.

After consideration of risks and benefits of intervention, it was decided to attempt to remove the thrombus, given significant risk for occlusion or further thromboembolism. The patient tolerated the procedure well and it was notable that the patient had subsequent improvement of inflammatory biomarkers. The pathology service received a 2.8×1.9×0.9 cm specimen designated intra-atrial septal patch inflammatory tissue. Grossly, cut sections of the specimen revealed a tan-pink to white cut surface with focal areas of possible purulent exudate. Representative sections are submitted for microscopic examination. Histological sections revealed endomyocardial tissue and patch material involved by both acute and chronic inflammation. The areas of chronic inflammation are characterised by dense fibrotic tissue with a florid chronic inflammatory infiltrate composed of a predominance of plasma cells and mature lymphocytes and only occasional neutrophils (figure 3A,B). Granulation tissue formation is

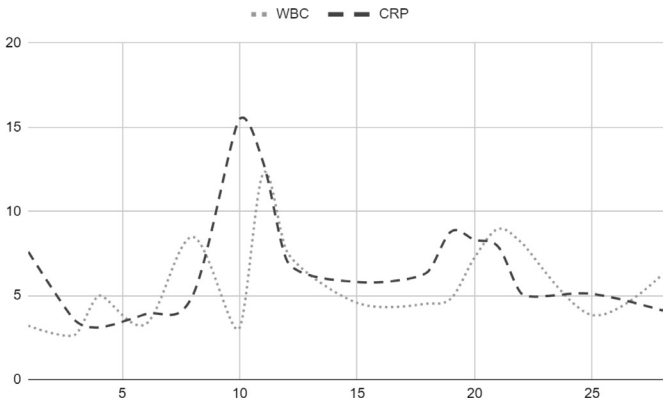

Figure 2 Temporal trend of WBC and CRP over hospitalisation. On day 1, intravenous immunoglobulin (IVIg) was administered and on day 8, the patient had her marantic lesion removed. The patient was started on antibiotics on day 9 of hospitalisation given uptrend in inflammatory markers for septic rule out given recent surgery and recurrence of fevers. CRP, C-reactive protein.

also appreciated. The acutely inflamed areas are characterised by a vegetative growth of predominantly necrotic tissue associated with a purulent exudate composed of aggregates of neutrophils admixed with fibrinous material (figure 3C). Several detached fragments of fibrinopurulent exudates contain clusters of neutrophils and associated fibrinoid material (figure 3D). Gram, GMS (grocotts methenamine (Gomori) silver) and periodic acid-Schiff (PAS) stains failed to demonstrate bacterial forms or fungi.

OUTCOME AND FOLLOW-UP

Our patient tolerated her procedures and after close clinical monitoring after cardiac intervention, she was deemed stable for discharge home to continue a full course of antibiotics for presumed bacterial endocarditis. She is clinically continuing to improve but is noted for difficulty with gait towards the latter half of the day/evening, but continues to work with both physical therapy and occupational therapy. Her speech is continuing to improve with engagement with speech therapy. She has had no recurrence of disease.

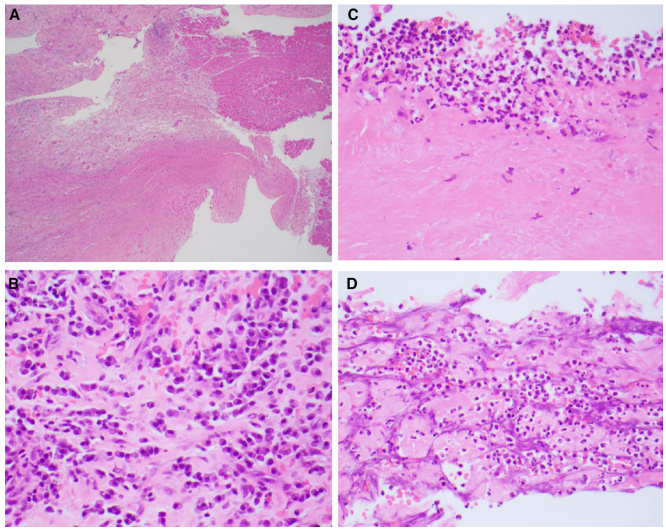

Figure 3 (A) Endomyocardial tissue with areas of large areas of fibrosis containing foci of dense chronic inflammation. (B) Chronically inflamed areas with numerous plasma cells in the background of dense fibrosis. Granulation tissue formation was also appreciated in these areas. (C) Area of vegetative growth with acute suppurative inflammation with numerous neutrophils overlying necrotic tissue. (D) Fragments of fibrinopurulent material are characterised by acute neutrophilic infiltrates associated with pink amorphous fibrinoid material. These fragments likely originated from the vegetative growth.

DISCUSSION

To our knowledge, this is the first report of a SARS-CoV-2 post-infectious inflammatory phenomenon in a child with unique features of inflammatory endocarditis and CVA complicating the case. This report is even more dramatic in the context of occurring in a child with DS, a population prone to both cardiac disease and immune dysregulation,[1 2 7–10] raising the possibility that this phenomenon could be observed in other children with either DS and/or prior abnormal cardiovascular structural physiology.

The patient had evidence of systemic inflammation, although the pathology observed in her heart was felt to be a prominent driver of disease. This inflammatory vegetative lesion, on pathological evaluation, was most similar to a Libman-Sacks endocarditis (LSE) as observed in persons with systemic lupus erythematosus or other autoimmune conditions that produce immune dysregulation.[11] Classic LSE is characterised by sterile accumulation of platelets and fibrin tissue within the endocardium, generally involving cardiac valves that can produce valvular insufficiency.[11] These lesions are prone to secondary infection as well as embolisation, which was felt to be the aetiology of this patient's CVA. Although there has not been a significant correlation with LSE in persons with DS, such patients are known to have immune dysregulation which could potentially place them at risk for marantic cardiac lesions under unique circumstances. The patient's inflammatory evaluation was notable only for elevations in non-specific biomarkers such as ESR and CRP, although the patient was noted to have low titre anticardiolipin antibodies (immunoglobulin A (IgA) and IgG). While this was not felt to be the primary aetiology of the patient's clinical presentation, especially in the setting of a negative anti-nuclear antibody (ANA) and double stranded DNA antibody (dsDNA), it was felt that these biomarkers may have represented the patient's inflammatory state. Of note, our patient had a normal echocardiogram 2 months prior to her hospitalisation, making an infectious or inflammatory endocarditis associated with primary SARS-CoV-2 infection significantly less likely. This is of particular relevance given the frequency of congenital cardiac disease necessitating repair in children with DS.

The role of immune dysregulation associated with DS is unclear in this case. It is well known and understood that patients with trisomy of chromosome 21 have immune dysregulation. This may either present itself as an increased susceptibility to infectious processes, such as frequent ear infection and upper respiratory infections, or produce autoimmune disorders, such as Hashimoto's thyroiditis, type I diabetes and coeliac disease.[9 12–16] Whether or not this predisposition towards infection may have lowered the threshold for primary infection with SARS-CoV-2 or post-infectious inflammatory phenomenon is unknown as there is no single clinical biomarker to prove this hypothesis.[3] In this patient, the suspicion was further increased given her dramatic improvement of symptoms after being administered immunomodulatory therapies via IVIg and intravenous methylprednisolone. Further, the lack of any infectious aetiology being identified in blood, CSF or on pathological examination further drives down the primary infection hypothesis.

During the COVID-19 pandemic, there has been a great deal of information regarding the post-infectious complications associated with primary SARS-CoV-2 infection in both patients with active signs and symptoms of infection and those who were considered asymptomatic.[17–19] Cerebrovascular and vascular issues in adult populations include hypercoagulable states that have produced significant CVA in otherwise healthy adults, acute respiratory distress syndrome, Guillain-Barre syndrome variants and myocarditis.[17–19] Thus far, there has been little in the way of reporting regarding endocarditis, or how this process impacts patients prone to immune dysregulation.

This case highlights an important potential complication in a vulnerable population. Children with DS have high rates of repaired congenital cardiac defects which may be more prone to inflammatory complications, acting as a nidus for the formation of a marantic vegetation. As this patient had a repair of her unbalanced AV canal, and the initial ASD patch and VSD patch were significantly affected by the vegetation in question, there should be careful consideration of paediatric patients with complex cardiac history that has been repaired as well as those with DS and other genetic syndromes that increase the risk of autoinflammatory conditions. As more information emerges regarding SARS-CoV-2 and its complications, physicians should remain vigilant when assessing patients who have a history of SARS-CoV-2 infection and new cardiac, neurologic or inflammatory/rheumatology symptoms. Although this is a single case, there may also be a potential role for the utilisation of immunomodulatory therapy in clinical situations such as the one presented.[20–23]

Learning points

- Children with Down syndrome (DS) are known to have immune dysregulation and a predilection for autoimmune disease, potentially increasing the risk for the development of post-infectious autoimmune phenomenon following primary infection with SARS-CoV-2.
- Very high rates of congenital heart disease in children with DS creates potential nidi for cardiac vegetations and may create a particularly susceptible location for marantic lesions following infection with SARS-CoV-2.
- In children with DS with unexplained fevers and inflammatory labs, detailed examination of the cardiac system is highly suggested.

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