BMH MEDICAL JOURNAL

BMH Med. J. 2022;9(1):19-22. **Case Series**

Autoimmune Manifestations Associated with COVID 19 Infection in Children: A Series of Three Cases From a Single Centre

Abdul Rauf, Mujeeb TM, Ajay Vijayan, Surya Antony Plathottathil, Sudhin Shylendran, Chellenton Jayakrishnan

Baby Memorial Hospital, Calicut, Kerala, 673004, India

Address for Correspondence: Dr Abdul Rauf KK, MD, FNB, Consultant Pediatric Intensivist, Department of Pediatrics, Baby Memorial Hospital, Calicut, Kerala, 673004, India. E- mail: abdrauf06@gmail.com

Abstract

Various immune-related manifestations are increasingly recognized in association with COVID-19. We describe a series of three pediatric cases, who presented with diverse autoimmune manifestations - Immune Thrombocytopenic Purpura, Nephrotic Syndrome and Autoimmune Encephalitis, which occurred 2-3 weeks after testing positive for SARS-COV-2 infection. During this pandemic, it might be appropriate to consider SARS-COV-2 testing (including antibodies) in children presenting with diseases of presumed autoimmune etiology.

Keywords: COVID-19, Autoimmunity, Immune thrombocytopenic Purpura, Nephrotic Syndrome, Autoimmune Encephalitis

Introduction

A multitude of diseases have been identified to have association with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Immune related disease manifestations are increasingly reported after infection with SARS-CoV-2. Till date, new onset of autoimmune diseases like systemic lupus erythematosus, Guillain-Barre syndrome and rheumatoid arthritis have been reported post SARS-CoV-2 infection in adults [1]. It is also now well established that SARS-COV-2 in children has led to an increase in cases of Multi System Inflammatory Syndrome-Children (MIS-C), an autoimmune phenomenon [2]. Reports of other autoimmune diseases in relation to SARS-COV-2 infection in children are scarce.

Herein, we describe a series of pediatric cases with various autoimmune manifestations (Immune thrombocytopenic Purpura (ITP), Nephrotic Syndrome, Seronegative Autoimmune Encephalitis (AE)) which occurred 2-3 weeks after testing positive for SARS-COV-2 infection.

Case 1

A pre-school previously well male child, presented with epistaxis after undergoing nasal swab for repeat Covid antigen testing, two weeks after testing PCR positive for SARS- COV-2. On evaluation, he was found to have thrombocytopenia (7000/mm^3) and was transfused with platelet concentrate and referred to authors' center. On examination, he had multiple petechial rashes over the body and in palate. He was hemodynamically stable and respiratory system examination was normal. He did not have lymphadenopathy or hepatosplenomegaly.

Initial complete blood count showed thrombocytopenia (15000/mm^3) and normal other cell lineages (hemoglobin-11.4 mg/dl and total leucokocyte count-9,400/mm^3). Peripheral smear was normal apart from marked thrombocytopenia and direct Coombs Test was negative. SARS Covid IgM antibody was positive and Anti-Nuclear Antibody (ANA) was negative. Possibility of ITP was considered and he was treated with IV Immunoglobulin (IVIg-1g/kg) along with other supportive measures. There was marked increase in platelet count (50,000/mm^3) after 24 hours of IVIg therapy which favored the diagnosis of ITP. Child remained well, there was no further bleeding manifestations and repeat platelet count on day 3 was 2.25 lakhs/mm^3. Child remained well on 6 weeks follow up (platelet count -3.5 lakhs/mm^3).

Case 2

A toddler male child presented with history of facial puffiness, abdominal distension and frothy urine for 4 days. He was tested PCR positive for SARS-COV-2 infection two weeks prior to the onset of these symptoms, had asymptomatic infection and was in home isolation. Respiratory system examination at admission was normal. There was periorbital puffiness, bilateral pitting pedal edema and ascites. Preliminary investigations showed nephrotic range proteinuria (urine spot protein creatinine ratio-17.5 mg/g and 24-hour urine protein 128mg/m^2/hour), no microscopic hematuria, with hypoalbuminemia (1.5 g/dl) and hyperlipidemia (total cholesterol- 450 mg/dl. Serum creatinine level (0.4 mg/dl), Antistreptolysin O (ASO) titer, serum C3 and C4 level were normal and ANA was negative. SARS-CoV-2 PCR was negative and Covid IgM antibody was positive. He was managed as first episode NS with oral steroids (prednisolone 2mg/kg/day), anti edema measures and other supportive measures. He improved clinically within a few days of initiation of steroid therapy and attained disease remission by day 8 and was discharged. He continued to be in remission, steroids were tapered gradually and stopped after 4 months. He remained asymptomatic and in disease remission four months after stopping steroids.

Case 3

An adolescent boy was in home isolation after testing PCR positive for SARS-COV-2 infection. He had mild symptoms like running nose in initial two days, which was managed with supportive medications, and he remained asymptomatic from day 3. Three weeks later, he developed instability while walking followed by slurring of speech and difficulty in swallowing. Over next two days, he developed altered sensorium in form of irrelevant talk and two episodes of seizures, and was referred to authors' center. Neurological examination showed encephalopathy (drowsiness) and features of brain stem involvement in form of absent gag reflex and cerebellar involvement (past pointing, intension tremors). His metabolic parameters (blood glucose, serum sodium, calcium, plasma ammonia and lactate) were normal.

Possibilities of acute meningoencephalitis and post-COVID AE were considered. IV antibiotics (ceftriaxone), anti-viral (acyclovir), IV antiepileptics and neuro-protective measures were started. Pulse steroids with IV methylprednisolone (1gm/day) was also started, considering AE as a differential diagnosis. Preliminary analysis of CSF showed mild pleocytosis (10 cells, all lymphocytes) with normal glucose and protein. Multiplex PCR (BioMerieux, USA) for neurotropic viruses (including Herpes simplex virus and Japanese Encephalitis virus) and bacteria in CSF was also negative. PCR for SARS-COV-2 in CSF was negative and COVID IgM antibody in serum was positive. Work-up for other tropical infections (Weil Felix, Widal test, dengue IgM) were also normal. Bedside EEG showed moderate diffuse electrical dysfunction. MRI Brain showed punctate foci of restricted diffusion in mid and lateral aspect of splenium of corpus callosum (**Figure 1**). Literature review showed similar reports of corpus callosal involvement in both COVID and post COVID Encephalitis. Autoimmune encephalitis panel of antibodies for GABA-B receptor, NMDA, CASPR 2, AMPA1 and AMPA 2) in CSF were normal. Child was treated as sero-negative autoimmune encephalitis and pulse methylprednisolone was continued. He showed improvement in neurological status, his sensorium improved within 24 hours, gag reflex and voice became normal by day 4 and started tolerating oral feeds. Pulse steroid was given for 5 days and was later changed to oral prednisolone. He was discharged after a week in neurologically normal condition and steroid dose was gradually tapered and stopped by 6 weeks. He remained well on 6 weeks follow up and repeat neuroimaging was normal.

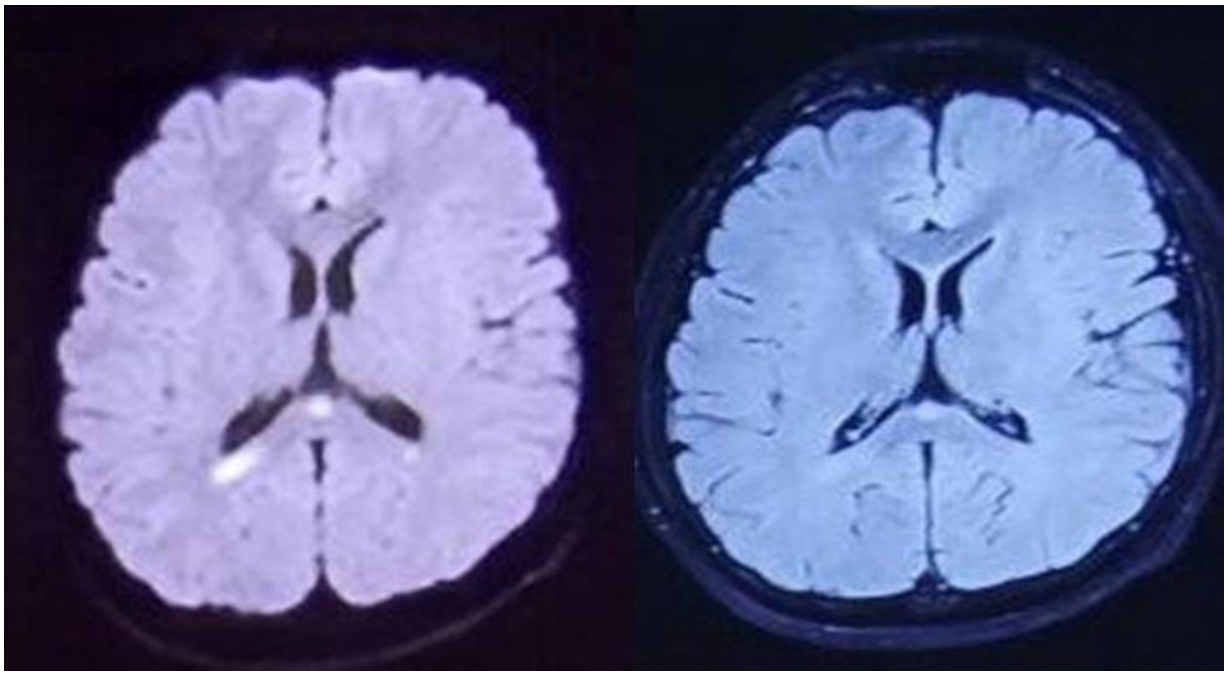

Figure 1: Diffusion Weighted Imaging and Apparent Diffusion Coefficient showing punctate foci of restricted diffusion/cytotoxic edema in mid and right lateral aspect of Splenium of Corpus Callosum.

Discussion

Various factors which contribute to the emergence of an autoimmune disease in a host include genetic predisposition, immune dysregulation, hormonal factors and environmental triggers like viral infections. Viruses may trigger autoimmunity by various mechanisms like structural or functional molecular mimicry, encoding proteins that induce cross-reactive immune responses to self-antigens and activation of B and T cells [3].

We described cases of three children, who presented with various autoimmune manifestation affecting different organ systems, probably triggered by COVID-19 infection. All of these cases had recent history of COVID infection, evident by positive COVID antibody (IgM) in serum.

It is well reported that ITP is often triggered by different viral infections. A temporal association between COVID-19 infection and ITP in a 65-year-old woman was reported by Zulfiqer et al [4]. A case of 9-year-old child who was diagnosed as ITP and had a history of SARS-CoV-2 infection 3 weeks before the onset of symptoms has also been published recently [5]. Like the patient in our series, these two cases also showed good response to IVIg therapy. There are only few reports of renal involvement in children associated with COVID-19. Kidney injury described in adult patients with severe COVID-19 ranges from microscopic hematuria, isolated proteinuria and azotemia, to acute kidney injury. Though the direct renal involvement due to SARS-COV-2 is less in children, they may present with illnesses related to abnormal immune response. Nephrotic syndrome (NS) is the most common immune mediated renal disease in children, which has been often reported previously with viral infections like H1N1. A case of new-onset NS in an 8-year-old boy has been recently reported in a pediatric patient diagnosed with COVID-19 infection [6]. Enya T et al reported a case of a 3-year-old boy, ho had recurrence of NS triggered by the SARS-CoV-2 infection [7]. Like the patient in our series, both of these cases responded well to treatment with prednisolone and it seems that the clinical presentation and course of NS associated with COVID-19 is not significantly different from NS associated with other viral infections.

Different neurological presentations associated with COVID-19 infections have been reported in children and adults. Most of these neurological manifestations are considered to be secondary to immune-mediated mechanisms, rather than neurotropism of the virus. Para infectious complications reported include AE, central nervous system demyelination and Guillain-Barre syndrome. Viral infections are one of the most common

precipitating factors in children for AE. Four cases of SARS-CoV-2-associated anti-NMDAR encephalitis in adults and one case in a child have been reported in literature [8]. Sarigecili et al reported a case of a 7-year-old boy, who presented with symptoms similar to patient in our series; acute ataxia and progressive encephalopathy in association with SARS-CoV-2 infection and was diagnosed with AE [9]. Like our patient, these patients didn't have in any respiratory or other systemic involvement and they responded well to pulse steroid therapy. Its also notable that a small series of four children with neurological symptoms associated with COVID-19 reported signal changes in the splenium of the corpus callosum (SCC), similar to our patient [10]. Reversible lesions of the SCC have been previously documented in patients with encephalopathies and are thought to be due to focal intramyelin edema secondary to inflammation. An association with COVID 19 should be suspected in children presenting with similar findings in neuroimaging during the pandemic.

Different kinds of immune-related manifestations are increasingly recognized in children, in association with COVID-19. In this pandemic scenario, it might be prudent consider SARS-COV-2 testing (PCR and antibodies) in children presenting with any disease, with a presumed autoimmune etiology or an infectious trigger. This may help the clinicians in establishing the etiology and provide relevant epidemiologic data. More studies and data are required to clearly delineate various autoimmune manifestations associated with SARS-COV-2 infection in children.

References

1. Sacchi MC, Tamiazzo S, Stobbione P, et al. SARS-CoV-2 infection as a trigger of autoimmune response. Clin Transl Sci. 2021;14:898-907.

2. Consiglio CR, Cotugno N, Sardh F, et al. The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. Cell. 2020;183:968-981.e7.

3. Getts DR, Chastain EM, Terry RL, et al. Virus infection, antiviral immunity, and autoimmunity. Immunol Rev. 2013;255:197-209.

4. Zulfiqar AA, Lorenzo-Villalba N, Hassler P, et al. Immune Thrombocytopenic Purpura in a Patient with Covid-19. N Engl J Med. 2020;382:e43.

5. Tsao HS, Chason HM, Fearon DM. Immune Thrombocytopenia (ITP) in a Pediatric Patient Positive for SARS-CoV-2. Pediatrics. 2020;146:e20201419.

6. Shah SA, Carter HP. New-Onset Nephrotic Syndrome in a Child Associated With COVID-19 Infection. Front Pediatr. 2020;8:471.

7. Enya T, Morimoto Y, Oshima R, et al. Nephrotic syndrome relapse in a boy with COVID-19. CEN Case Rep. 2021;10:431-434.

8. Ramos-Casals M, Brito-Zeron P, Mariette X. Systemic and organ-specific immune-related manifestations of COVID-19. Nat Rev Rheumatol. 2021;17:315-332.

9. Sarigecili E, Arslan I, Ucar HK, et al. Pediatric anti-NMDA receptor encephalitis associated with COVID-19. Childs Nerv Syst. 2021;1-4.

10. Abdel-Mannan O, Eyre M, Lobel U, et al. Neurologic and Radiographic Findings Associated With COVID-19 Infection in Children. JAMA Neurol. 2020;77:1440-1445.