COVID-19 AND ACUTE DEMYELINATING CENTRAL NERVOUS SYSTEM DISORDERS IN CHILDREN

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Abstract

Background: Neurological manifestations of SARS-CoV-2 infection are increasingly being recognized. If we focus on the coronavirus family, there is clear evidence of its neurotropic character as demyelinating disease has been previously reported with MERS (Middle East respiratory syndrome) and SARSCoV-1. **Aim of the work:** Is to evaluate the possible role of COVID-19 in the development of acute demyelinating CNS disorders. **Material & methods:** Observational Cross-sectional study of Pediatric Patients who have acute demyelinating CNS disorder, presenting to Cairo university children's hospital over the period of 18 months from June 2020 till June 2021 with their follow-up over a period of at least 6 months till December 2021. We enrolled in our study 41 subjects who have acute demyelinating CNS disorder, 3 patients were diagnosed as Acute disseminated encephalomyelitis (ADEM), 4 as Acute necrotizing encephalopathy of childhood (ANEC), 1 as Multiphasic ADEM (MADEM), 14 as Neuromyelitis optica spectrum disorder (NMOSD), 8 as Multiple sclerosis (MS), 4 as optic neuritis (ON), and 7 as transverse myelitis (TM). the patients were evaluated clinically, radiologically and labs were done including COVID-19 antibodies (both serum IgM and IgG), that were done for the patients at their presentation and during follow-up. **Results:** In our study we found that 4.8% of ADEM patients, 14.3% of ANEC patients, 28.6% of NMOSD patients, 19% of MS patients, 19% of ON patients and 14.3% of TM patients were tested positive for COVID-19 immunoglobulins but with no significant statistical correlation. We found that there was a correlation between serum COVID-19 IgG seropositivity and motor weakness as a presenting symptom and between COVID-19 IgG seropositivity and need for ICU admission. On correlating the serum seropositivity for COVID-19 IgG with MRI findings we found a correlation between COVID-19 IgG seropositivity and thickened optic nerves in patients diagnosed with ON, NMOSD and MS. **Conclusion:** Seropositivity for COVID-19 antibodies was found among the patients of different groups of acute demyelinating CNS disorders, but a causative relationship cannot be established yet.

Keywords: COVID-19, CNS demyelinating diseases, pediatric patients.

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1-INTRODUCTION:

The neurological manifestations of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection responsible for the current worldwide coronavirus disease 2019 (COVID-19) pandemic were observed including immune-mediated demyelinating disorders of the central and peripheral nervous systems have been reported in a few studies in the adult population (**Khair., 2022)**.

Isolated reports of acute demyelinating encephalomyelitis (ADEM), transverse myelitis (TS) and Guillain Barre Syndrome (GBS), for instance, are almost exclusively confined to adults. However, reports of particular correlation with the onset of CNS demyelinating disorders are sparse in the pediatric age group. Nevertheless, it is plausible to hypothesize that acute COVID-19 infection can trigger a series of immune-mediated sequelae in children, which may include various CNS demyelination syndromes (**Khair., 2022)**.

However, data remains limited in terms of cases of CNS post-infectious demyelinating/inflammatory disease following COVID-19. Recent studies have shown that the novel coronavirus appears to cross the

blood-brain barrier and cause acute or delayed CNS demyelination or axonal damage **(Desforges et al., 2020).**

A variety of mechanisms have been postulated including virus-induced hypercoagulable or pro-inflammatory states, direct viral invasion of the CNS, and post-infectious immune mediated processes. The first radiologic description of neurologic complications due to SARS-CoV-2 infection was described by **Poyiadji et al.** with a case of acute necrotizing encephalopathy (ANE), probably related to virus-induced cytokine storm. For SARS CoV-2 infection, the pro-inflammatory state induced by the cytokine storm, mainly sustained by IL-1, IL-6, and TNF-α, may be responsible for the activation of glial cells with subsequent demyelination **(Poyiadji et al., 2020)** (**Mehta et al., 2020).**

A possible alternative could be the production of antibodies against glial cells triggered by the virus, as a para-infectious or post-infectious phenomenon. Coronaviruses have been associated with other demyelinating pathologies like acute or subacute disseminated encephalomyelitis (ADEM) in humans **(Yeh et al., 2004).** ADEM is a rare acute inflammatory demyelinating disease that may follow viral infections. The first case of COVID-19 associated ADEM was described in a 40-year-old woman **(Zhang et al., 2020).**

Another case of ADEM was reported in a 54-year-old woman following COVID-19 disease. SARS-CoV-2 was not detected in the CSF probably because the neurological damage was sustained by a delayed immune response occurring after the viremia **(Zanin et al., 2020).** The first reported case of SARS-CoV-2 causing acute transverse myelitis was reported from Wuhan,China, where the outbreak first began, and the second case from Boston **(Zhao et al., 2020 and Sarma et al.,2020).**

SARS-CoV-2 may play a role of infective trigger, similar to the one of Epstein Barr virus in MS. The presence of demyelination, as well as SARS virus particles and genome sequences, in the brain has been detected in autopsy studies **(Zhang et al., 2003).**

2- MATERIAL & METHODS:

This is a single center descriptive study conducted at the neuropediatric unit of Cairo University children ‘s hospital over the period of 18 months between June 2020 and December 2021.

Study Population:

The study was carried out on 41 patients of either sex or ages between 1 year and 14 years. Cases were selected for having an acute demyelinating CNS disorder. Patients presented to the casualty of Cairo University children ‘s hospital then followed up at neuropediatric outpatient clinic. The study was approved by the scientific and ethical committee at faculty of medicine with approval no MD-234-2020, Cairo University. Informed verbal consent was taken from the parents.

METHODS:

All cases enrolled were subjected to full history taking, thorough neurological examination, radiological assessment (including MRI brain and when myelitis was suspected clinically MRI spine was done) and laboratory evaluation.

Laboratory investigations included Anti-MOG and Antiaquaporin-4 antibodies for all patients. Oligoclonal bands in CSF samples were done for patients suspected to have MS. Additionally, virology screen for COVID-19 (IgM) and (IgG) in serum sample was done for all patients as the most of the study took place during the Covid-19 pandemic.

MRI brain as well as MRI spine for patients presenting with myelitis was done once suspected clinically. VEP was also done for the patients presented with visual affection.

Follow-up of patients after 6 months from disease onset involved both comprehensive clinical, radiological and laboratory workup.

STATISTICAL ANALYSIS:

Data was presented using range, mean and standard deviation (SD) for parametric data, while non-parametric data was described using range, median and interquartile range (IQR) for quantitative variables and frequency and percentage for qualitative ones. Comparison between groups was performed using Kruskal Wallis or Mann Whitney test for quantitative variables and Chi square or Fisher's exact test for qualitative ones. Spearman correlation coefficients were calculated to assess the correlation between different quantitative variables. Change of quantitative or ordinal variables over time was investigated through Wilcoxon test while that of binary variables was assessed through McNemar test P-values less than 0.05 were considered statistically significant.

3- RESULTS:

On measuring the serum COVID-19 immunoglobulins among the patients diagnosed with ADEM at the first presentation we found that one patient (33.3 %) was positive for IgG, and no one was positive for IgM. While on measuring the serum COVID-19 immunoglobulins among the patients diagnosed with ANEC at the first presentation we found that three patients (75%) were positive for IgM while none of them was positive for IgG. Serum immunoglobulins for COVID-19 were done for the

patient diagnosed with multiphasic ADEM and it was negative for both IgG and IgM.

Table (1): Serum COVID-19 immunoglobulins among the patients diagnosed with ADEM, ANEC and Multiphasic ADEM at the first presentation.

	ADEM(N=3)	**ANEC(N=4)**	**MADEM(N=1)**
COVID-19 Ig G			
Positive	1 (33.3)	0 (0)	0(0)
Negative	2 (66.7)	4 (100)	1(100)
COVID-19 Ig M			
Positive	0 (0)	3 (75)	0(0)
Negative	3 (100)	1 (25)	1(100)

On measuring the serum Covid-19 immunoglobulins among the patients diagnosed with NMOSD at the first presentation we found that 28.6 % were positive for IgG and 21.4 % were positive for IgM.

Table (2.1): Serum COVID-19 immunoglobulins among the patients diagnosed with NMOSD at the first presentation.

	Neuromyelitis Optica spectrum disorder (N=14)
COVID-19 Ig G	
Positive	4 (28.6)
Negative	10 (71.4)
COVID-19 Ig M	
Positive	3 (21.4)
Negative	11 (78.6)

Only one (7.1%) of the patients diagnosed with NMOSD was positive for COVID-19 IgM.

Table (2.2): Follow-up of the serum COVID-19 immunoglobulin levels among the patients diagnosed with NMOSD.

	Neuromyelitis optica spectrum disorder (N=14)
COVID-19 Ig G	
Positive	0 (0)
Negative	14 (100)
COVID-19 Ig M	
Positive	1 (7.1)
Negative	13 (92.9)

On measuring the serum COVID-19 immunoglobulins among the patients diagnosed with MS at the first presentation we found that 37.5 % were positive for IgG and 25 % were positive for IgM.

Table (3.1): Serum COVID-19 immunoglobulins among the patients diagnosed with MS at the first presentation.

	Multiple sclerosis (N=8)
COVID-19 Ig G	
Positive	3 (37.5)
Negative	5 (62.5)
COVID-19 Ig M	
Positive	2 (25)
Negative	6 (75)

During following up the patients diagnosed with MS three (37.5%) of them were positive for COVID-19 IgG and all were negative for IgM.

Table (3.2): Follow-up of the serum COVID-19 immunoglobulin levels among the patients diagnosed with MS.

	Multiple sclerosis (N=8)
COVID-19 Ig G	
Positive	3 (37.5)
Negative	5 (62.5)
COVID-19 Ig M	
Positive	0 (0)
Negative	8 (100)

On assaying the serum COVID-19 immunoglobulins among the patients diagnosed with ON at the first presentation we found that all the patients were positive for IgG and one patient(25 %) was positive for both IgG and IgM.

Table (4.1): Serum COVID-19 immunoglobulins among the patients diagnosed with ON at the first presentation.

	Optic neuritis (N=4)
COVID-19 Ig G	
Positive	4 (100)
Negative	0 (0)
COVID-19 Ig M	
Positive	1 (25)
Negative	3 (75)

During following up the patients diagnosed with ON one patient (25%) was positive for COVID-19 IgG (the patient who had the recurrence).

Table (4.2): Follow-up of the serum COVID-19 immunoglobulin levels among the patients diagnosed with optic neuritis.

	Optic neuritis (N=4)
COVID-19 Ig G	
Positive	1 (25)
Negative	3 (75)
COVID-19 Ig M	
Positive	0 (0)
Negative	4 (100)

On assaying the serum COVID-19 immunoglobulins among the patients diagnosed with TM at the first presentation, we found that 28.6 % were positive for IgG and 14.3 % were positive for IgM.

Table (5.1): Serum COVID-19 immunoglobulins among the patients diagnosed with TM at the first presentation.

	Transverse myelitis (N=7)
COVID-19 Ig G	
Positive	2 (28.6)
Negative	5 (71.4)
COVID-19 Ig M	
Positive	1 (14.3)
Negative	6 (85.7)

During following up the patients diagnosed with TM 14.3% of them were positive for COVID-19 IgG.

Table (5.2): Follow-up of the serum COVID-19 immunoglobulin levels among the patients diagnosed with TM.

	Transverse myelitis (N=7)
COVID-19 Ig G	
Positive	1 (14.3)
Negative	6 (85.7)
COVID-19 Ig M	
Positive	0 (0)
Negative	7 (100)

We found that there is a correlation between serum COVID-19 IgG seropositivity and weakness as a presenting symptom with a P-value 0.035.

Table (6): Correlation between COVID-19 (IgG) immunoglobulins seropositivity and different presenting symptoms.

		COVID-19 immunoglobulins (IgG)				**P-value**
		Positive		**Negative**		
		Count	**%**	**Count**	**%**	
Encephalopathy	**Positive**	1	7.1%	9	33.3%	0.123
	Negative	13	92.9%	18	66.7%	
Motor weakness	**Yes**	9	64.3%	25	92.6%	0.035
	No	5	35.7%	2	7.4%	
Urinary incontinence	**Yes**	9	64.3%	19	70.4%	0.734
	No	5	35.7%	8	29.6%	
Acute vision loss or blurring of vision	**Yes**	9	64.3%	12	44.4%	0.228
	No	5	35.7%	15	55.6%	

On correlating the serum seropositivity for COVID-19 IgG to the different MRI findings we found a correlation between COVID-19 IgG seropositivity and thickened optic nerves in which we found that ten patients who had thickening of the optic nerves were tested positive for COVID-19 IgG with a P-value 0.037.

Table (7): Correlation between COVID-19 (IgG) immunoglobulins seropositivity and different MRI brain and spine findings.

		COVID-19 immunoglobulins (IgG)				**P value**
		Positive		**Negative**		
		Count	**%**	**Count**	**%**	
White Matter (MRI BRAIN) site	**Normal**	11	78.6%	15	55.6%	0.147
	Affected	3	21.4%	12	44.4%	
Basal Ganglia (MRI BRAIN) site	**Normal**	13	92.9%	23	85.2%	0.645
	Affected	1	7.1%	4	14.8%	
Thalamus (MRI BRAIN) site	**Normal**	13	92.9%	20	74.1%	0.227
	Affected	1	7.1%	7	25.9%	
Cerebellum (MRI BRAIN) site	**Normal**	13	92.9%	17	63.0%	0.064
	Affected	1	7.1%	10	37.0%	
Brain Stem (MRI BRAIN) site	**Normal**	13	92.9%	18	66.7%	0.123
Optic Nerve (MRI BRAIN) site	**Thickened**	10	71.4%	10	37.0%	0.037
	Normal	4	28.6%	17	63.0%	

We found a correlation between COVID-19 IgG seropositivity and the need for ICU admission with a P value 0.021.

Table (8): Correlation between COVID-19 (IgG) immunoglobulins seropositivity and need for ICU admission.

	COVID-19 immunoglobulins (IgG)				**P value**
	positive		**negative**		
	Count	**%**	**Count**	**%**	

Need for ICU admission	**Yes**	3	21.4%	16	59.3%	0.021
	No	11	78.6%	11	40.7%	

4- DISCUSSION:

Acquired demyelinating syndromes (ADS) is an umbrella term that encompasses a wide spectrum of inflammatory and demyelinating disorders of the central nervous system (CNS). ADS are exceedingly rare in children, with an estimated annual incidence of 0.6–1.66 cases per 100,000 children **(Ketelslegers et al., 2012 and Kilic et al., 2021).**

In 2012, several subcategories including multiple sclerosis (MS), monophasic acute disseminated encephalomyelitis (ADEM), multiphasic ADEM, neuromyelitis Optica spectrum disorder (NMOSD), and clinically isolated syndrome (CIS) were addressed by the International Pediatric Multiple Sclerosis Study Group (IPMSSG) to improve consistency in the terminology of clinical and basic research **(Krupp et al., 2013 and Kilic et al., 2021).**

This study was undertaken to evaluate the relationship between COVID-19 infection and acute demyelinating central nervous system disorders in the patients who presented to Cairo University Children's Hospital from the period of June 2020 to December 2021.

This study was carried out on 41 patients, twenty patients (48.8%) were males and twenty-one patients 51.2% were females.

Fourteen patients (34.1%) were diagnosed with neuromyelitis Optica spectrum disorder, eight patients (19.5%) with multiple sclerosis, seven (17.1%) with transverse myelitis, four patients (9.8%) with optic neuritis, four (9.8%) ANEC, three (7.3%) ADEM, one (2.4%) MADEM.

All these patients had their first presentation at Cairo university Children's Hospital casualty admitted to the inpatient units and then they followed up at neurology outpatient clinic.

Preceding viral and bacterial infections may induce the development of ADS, particularly acute disseminated encephalomyelitis which usually follows an infection of the upper respiratory tract. Numerous pathogens have been associated with acute disseminated encephalomyelitis. For instance, viruses that have been implicated in this disorder include measles, rubella, varicella, influenza, and Epstein - Barr virus, Coxsackie virus, coronavirus, human immunodeficiency virus, herpes simplex, cytomegalovirus, and West Nile virus **(Özkale et al., 2012).**

In this study, a history of antecedent infection was reported in 39 patients (95.1%). The serologically proven infectious agent was COVID-19.

COVID-19 immunoglobulins were done for the patients at their first presentation for both IgM and IgG and it was found that 14 patients (34.1%) were positive for IgG and 10 patients (24.4%) were positive for IgM. Other studies like **Kilic et al.** found out that the infectious agent was EBV in one ADEM patient. However, another patient experienced the first clinical ADEM episode during the skin rashes related to varicella **(Kilic et al., 2021).**

In this study, we found that the percentage of seropositivity for COVID-19 immunoglobulins (either IgM or IgG) at the first presentation was 33.3% (N=1) in ADEM patients, 75% (N=3) in ANEC patients, 50% (N=7) in NMOSD patients, 62.5%(N=5) in MS patients, 100%(N=4) in ON patients and 42.8% (N=3) in TM patients, but with no statistical significance. Unlike **Ismail et al.,** the study that has shown an association between COVID-19 infection and the development of different types of CNS demyelination, the most frequent type was post-infectious, immune-mediated ADEM-like presentation, followed by TM, suggesting that a probable para-infectious or post-infectious immune-mediated etiology might be implicated in patients with Covid-19 (**Ismail et al., 2022).**

Hussein et al., reported that acute systemic COVID-19 infection seems to exacerbate pre-existing ADEM symptoms in some patients **(Hussein et al., 2020).**

Kaur et al., reported post COVID-19 infection TM cases. Ghosh et al., reported cases with longitudinally extensive TM, and seropositivity for AQP4 antibody following acute COVID-19 pneumonia **(Kaur et al., 2020) (Ghosh et al., 2020).**

We found that there is a correlation between serum Covid-19 IgG seropositivity and motor weakness as a presenting symptom and also between Covid-19 IgG seropositivity and the need for ICU admission, unlike **Ismail et al.,** who found no association between Covid-19 severity and different types of CNS demyelinating diseases severity at hospitalization, suggesting an immune-mediated mechanism independent of the intensity of the initial immune response **(Ismail et al., 2022).**

On correlating serum seropositivity for Covid-19 IgG with MRI findings we found a correlation between Covid-19 IgG seropositivity and thickened optic nerves that came in agreement with Jossy and coworkers **(Jossy et al., 2022).**

We found no association between Covid-19 infection and different MRI brain and spine findings other than thickening of the optic nerves which was found in

71.4% (N=10) of the seropositive patients for Covid-19 antibodies, which came in agreement with Klironomos et al., a study that noted Prominent subarachnoid spaces around the optic nerves in 56% of their patients on T2-weighted MRI sequences. **(Klironomos et al., 2020).**

Román et al., found a correlation between the findings of MRI spine that was done for the patients presented with TM and COVID-19 infection, in which the cervicothoracic spinal cord was the most affected segment with demyelinating lesions among their patients **(Román et al., 2021)**.

5- CONCLUSION:

Seropositivity for COVID-19 antibodies was found among the patients of different groups of acute demyelinating CNS disorders, but a causative relationship cannot be established yet.

6- LIMITATIONS:

This study had some limitations such as small sample size, time, and resources, and further studies are required including a large sample size and more investigation like PCR for COVID-19 for better evaluation of the relationship between COVID-19 and acute demyelinating CNS disorders in children.

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