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Spectrums of neurological manifestations of COVID-19 in children and its immediate and long term outcome: Experience of the largest pediatric COVID unit of Bangladesh

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Abstract:

Background: *SARS Cov-2 infection presented with mild respiratory illness but has evidence of multisystem involvement in little percentage, though severity of infection is less in children. Neurological manifestations may vary from headache, dizziness, olfactory or taste dysfunction to specific syndromes including meningitis, stroke, acute transverse myelitis, ADEM and Guillain-Barre syndrome. But there is little evidence worldwide about neurological complications of COVID-19 in children.*

Methods: *This longitudinal study was carried out in COVID unit of Dhaka medical college among the children age 1 month to 14 years, who were positive for covid-19 RT-PCR and presented with neurological features with further follow up for a period of 6 months.*

Results: *Among 539 COVID confirmed cases 53 (9.83%) were presented with neurological manifestations; mean age of the patient's was 64.09±43.09 months with male predominance. Among the studied population 35(66%) cases presented with features of meningoencephalitis, 6(11.3%) with febrile seizures, 4(5.6%) with GBS. Acute stroke syndrome, transeverse myelitis, ADEM and autoimmune encephalitis 2(3.8%) cases from each. Three (7.5%) cases expired. At the end of follow up only 3 cases found with neurological complications, one with epilepsy and two had residual motor weakness.*

Conclusion: *Neurological involvement of COVID-19 in children is not uncommon, early suspicion and intervention is crucial to limit the mortality and morbidity.*

Key words: *Post COVID-19 infection, Neurological manifestation, Meningo-encephalitis, ADEM, GBS, TM.*

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Introduction:

Most of the children with COVID-19 remain asymptomatic, percentage of case detection among the children is less and it's about 7-8% of total.[1] There are multiple reports of atypical symptoms in children worldwide, neurological manifestations is one of them, Children younger than 18 years have more neurological symptoms in COVID-19 infection. United States have reported around 3,700 cases among them 17% had nonspecific neurologic conditions such as headache, fatigue, and myalgia, and 1% presented with encephalopathy, seizures, and meningeal signs.[2] Similarly worldwide a report of nearly 1,400 pediatric patients also presented with headache (4%), anosmia (2%), seizures (0.7%), and cerebrovascular stroke (0.7%) related to COVID-19 infection.[3] Child may present with these features without having any classical features of COVID. Behind the neurological manifestations related to COVID infection there are two hypothesis considered, one is based on a retarded multisystemic inflammatory response to the viremia. This uncontrolled inflammatory state leads to the multi-organ damages related to release of inflammatory agents leading to a cytokine storm causing the disruption of the integrity of the BBB allowing various molecules (tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-12, and interferon-gamma (INFγ) to penetrate into the brain. The second

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hypothesis based on post infectious immune-mediated mechanisms: SARS-CoV-2 initiate an autoimmune response by activating antibodies against brain components or *via* "molecular mimicry" the spike protein of the SARS-CoV-2 that may cross-react with CNS components explaining some of the neurologic complications like Guillain Barré-syndrome (GBS), acute disseminated encephalomyelitis (ADEM) or autoimmune encephalitis.[4,5,6] Neurological manifestations can also be caused or aggravated by hypoxemia, septic shock, metabolic or electrolyte disorders related to COVID-19 infection.[7] Children has less severe form of SARS-CoV-2 infection compared to adults because children have less co morbidities like hypertension, smoking, hypercholesterolemia, obesity etc. and the host immune response in children is more efficient than in adults like increased number of adaptive immunity cells CD4+/CD8+, better functional capacity of B-cells, and the trained innate immunity.[8] For this reason mortality rate of children has been reported under 0.1% with about 2% of children need to admit in intensive care units.[9] But there is no enough data about neurological complications of COVID-19 in children in Bangladesh. Recognition of uncommon disease presentations is necessary to protect our children in terms of mortality and morbidity

Methods & Materials:

This longitudinal observational study was carried out on the child corona unit of Dhaka Medical College Hospital (largest child corona unit of Bangladesh) during period of June 2020 to June 2022, total 53 patients between ages of 1 month to 14 year of confirmed COVID-19 positive case proved by RT-PCR test with different neurological manifestations like convulsion, altered sensorium, headache, focal neurological signs, abnormal movements, psychiatric manifestations etc. were included in this study. Children with co morbidities like malignancy, renal diseases or any congenital malformations and those are non-compliant to be followed up were excluded from the study. All clinical information's and results of relevant investigations were collected. All the children were followed up monthly for further 6 months to assess their immediate and long term outcome. All information was collected in a preformed semi structured questionnaire. Data were processed and analysed by using computer software SPSS (Statistical Package for Social Science) version 23.

Results:

During period of June 2020 to June 2022, total 1281 patients were suspected for COVID infection among them 339 were virologically confirmed, Fifty two (52) patients had neurological co morbidities, Fifty three (53) had neurological manifestations and these patients with neurological manifestations were followed up monthly for further 6 months to see their immediate and long term outcome.

Table I

Demographic characteristics of studied population

Demographic Characteristics of patient	Number (%)
Age	
< 1 month	25 (7.4)
1 month- up to1 year	86(25.2)
1 year – up to 5 year	96(28.2)
5 year – up to 14 year	132(39.1)
Sex	
Male	220 (65)
Female	119(35)
Resident	
Urban	84 (24.7)
Rural	255 (75.3)
Socioeconomic status	
<20,000 taka/ month	31(9.1)
20,000-50,000 taka/ month	174(51.6)
> 50,000 taka/ month	134(39.3)

Here majority of our patients from age above five years, and from rural area of lower middle class background.

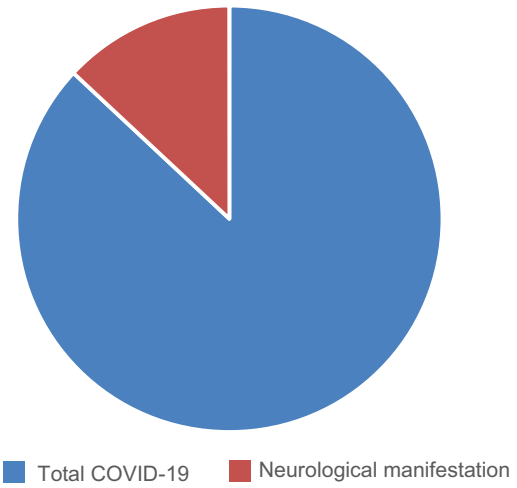

Figure 1: *Percent of children with SARS-CoV-2 infection with neurological manifestation*

Among the total SARS-CoV-2 positive cases 15% of them presented with neurological manifestation (Figure -1).

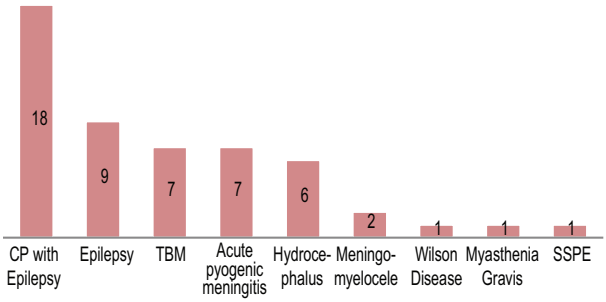

Figure 2 : *Distribution of COVID-19 Positive children according to their Neurological comorbidities (n-52)*

Patient with cerebral palsy and epilepsy were most commonly suffered from COVID-19 infection during this pandemic (Figure 2).

Table II

Distribution of studied population according to neurological presentation (n-53)

Common Neurological Presentation	Number (%)
Meningoencephalitis	35(66)
Febrile seizure	06(11)
GBS	04(7.5)
Acute Stroke Syndrome	02(3.8)
Transverse Myelitis	02(3.8)
ADEM	02(3.8)
Autoimmune encephalitis	02(3.8)

Most frequent neurological disorder associated with COVID-19 infection was meningoencephalitis and next common was febrile seizure (Table II).

Table III

Clinical presentation of studied population (n-53)

Clinical presentation	Number (%)
Fever	48(90.7)
Altered sensorium	32(60.4)
Convulsion	31(58.5)
Unconsciousness	22(41.50
Headache	19(35.9)
Speech Problem	10(18.9)
Hemiplegia	10(18.9)
Paraplegia	07(13.2)
Vomiting	06(11.3)
Visual disturbance	04(7.5)
Autonomic disturbances	04(7.5)
Psychiatric manifestation	03(5.7)

Fever, altered sensorium, convulsion, unconsciousness was found as common presentation among the studied population (Table III).

Table IV

Laboratory parameter of studied population

Laboratory Parameter	Results(mean±SD)	Number (%)
Hematological Parameters		
Hemoglobin level(gm/dl)	10.5±2.2	53(100)
Leucocyte count/cmm3	7540± 6108	53(100)
Neutrophil count/ cmm3	890± 735	53(100)
Lymphocyte count/ cmm3	1070± 879	53(100)
Platelet count/ cmm3	1,76,231±1,08,389	53(100)
Inflammatory marker		
C-reactive protein(CRP)mg/L	131±102	45(85)
D- dimer, ng/ml	11,545± 10,324	38(71.7)
S. Ferritin, ng/ml	4689±4,301	38(71.7)
Fibrinigen, mg/dl	489±276	38(71.7)
Procalcitonin, ng/ml	0.2±0.18	20(38)
Troponin-I, ng/ml	0.09±0.075	20(38)

Table IV (Cont'd)

Laboratory parameter of studied population

Laboratory Parameter	Results(mean±SD)	Number (%)
Radiographic findings		
Chest x-ray	Abnormal	41(77.4)
Chest CT	Abnormal	35(66)
CSF study		
Color	Clear	42(79)
Cell count,cmm3	06±06	42(79)
Protein,gm/dl	78±45	42(79)
Glucose gm/dl	36±12	42(79)
Chloride, mEq/L	115±13	42(79)
LDH, mmol/L	1.70±0.8	32(60.4)
Gram staining	Negative	42(79)
Autoimmune antibody	Negative	01(1.8)
Neuroimage (CT/MRI)	Atrophy	32(80)
	Infarction	05(12.5)
	Meningeal enhancement	28(70)
	Demyelinating lesion	2(5)
	Hyperintensity	2(5)
	Hemorrhage	1(2.5)
NCS (Nerve Conduction Study)	AMAN	3(75)
	AMSAN	1(25)

Investigations was done according to the clinical presentation to confirm diagnosis and for management purpose

Table V

Immediate outcome of studied population (n-53)

Immediate outcome	Number (%)	Diagnosis	Number (%)
Discharge with advise	44(83)	Complete recovery	32(60.3)
		Motor disability	12(22.6)
		Speech problem	05(9.4)
		Memory loss	02(3.8)
		Seizure	02(3.8)
Discharge with request	04(7.5)	Complete recovery	04(7.5)
Death	3(5.6)	Meningoencephalitis	02(3.8)
		Hemorrhagic stroke	01(1.9)
Absconded	02(3.8)	Not became available for follow up	02(3.8)

Majority of our studied population achieved complete recovery within 15 to 21 days of admission, patients with different disabilities (n-21) were followed up monthly for further 6 months to assess their long term outcome (Tabe V).

Table VI
Late outcome of studied population (n-21)

Late outcome (n-21)	Number (%)
Complete recovery	18 (34.0)
Mild motor disability (level-II)	02 (3.8)
Moderate motor disability (level-III)	01 (1.9)

According to GMFCS only 3 patients had mild to moderate motor disabilities, eighteen patients recovered completely.

Discussion:

The SRAS-CoV-2 infection is the global health crisis that was initially focused on only respiratory symptoms but later on it is documented to present with complex clinical picture and neurological manifestations is one of them[9]. The fact about COVID-19 infection in children that they are presented with less severe form than adults and overall estimated mortality rate less than 0.1%. Patients needed intensive care is around 2%[10]. The reason behind the difference from adult as the children has less co morbidities and they usually do not suffer from pro-inflammatory state that are contributed by hypertension, smoking, hyper-cholesterolemia etc.[11] In this study from total COVID-19 positive cases 14.5% of them presented with neurological comorbidities and 15% had neurological manifestations, Among the co morbid condition patient with cerebral palsy and epilepsy was the most vulnerable patient to suffer from COVID-19 infection.

Meningoencephalitis is the inflammation of brain and its covering usually caused by direct viral invasion, post infectious immune mediated polyradiculopathy like GBS or demyelination like ADEM, Autoimmune encephalitis, Transverse myelitis etc. is the most common neurological complications of SARS-CoV-2 infection. In this cohort among the total 53 cases, sixty six percent (66%) presented with meningoencephalitis with features of fever (90.7%), altered consciousness (60.4%), convulsion (58.5%) and headache (35.9%). Study done by Sung-Min Cho et al finds that seizure was more frequent in children (3.0%) than in adults (1.0%); reported in-hospital, [12] seizures decreased with increasing age, the frequency of stroke increased with increasing age. In contrast, CNS infection and seizure proportions steadily decreased with increasing age.

Post COVID Immune mediated disorder like GBS, ADEM, Transverse myelitis and autoimmune encephalitis presented with same features as other post infectious etiology,

Regarding general routine investigations a neutrophil lymphocyte ratio (NLR) > 3 has been reported as an independent predictor of neurological manifestations[13] which was not assessed in this study but presence of lymphocytosis, high level of inflammatory marker like CRP, S. ferritin, D-dimer, Procalcitonin levels was most common laboratory findings observed here. CSF RT-PCR was negative in all cases where it was recommended to do, albuminocytological dissociation observed in patients with polyrediculopathy in other cases protein level was found mildly elevated. Lymphocytic pleocytosis was the common CSF findings in the patients with features of meningoencephalitis, autoimmune encephalitis and transverse myelitis. Pilotto et al, AlKetbi et al and Zhao et al have the same observations[14,15,16]. Post COVID polyradiculopathy or Guillain Barre Syndrome was reported total four in number during study period, nerve conduction study (NCS) was classified the types of GBS and here we found 75% was AMAN variety, and 25% was AMSAN. Study done by Abu-Rumeileh et al they have found NCS in COVID-19-related GBS cases predominantly demyelinating involvement in five, axonal in five, and mixed pattern in a single case[17]. Neuroimage mostly MRI of brain that was done in our patients revealed leptomeningeal involvement, cortical and subcortical infarction and cortical atrophy were most common and consistent findings of patients with meningoencephalitis, Moriguchi et al, Duong et al, and Wong et al they also reported same findings in their study[18,19,20]. Demyelinating lesion and T2 hyperintense lesion was observed in four cases and hemorrhage was found in one case in this group.

Symptomatic management including oxygen therapy was the mainstay of management, syndrome specific management was also initiated as per protocol. Antiviral drugs, and anti-thrombotic agents was also prescribed in specific situations. With all conventional management we lost our three patients during treatment period two of them were diagnosed as meningoencphalitis and one of them was hemorrhagic stroke. Thirty six (68%) cases was discharged with complete recovery, motor disability was the most common morbidities was noticed during discharge

among 23% of cases, speech difficulty(9.4%), memory loss(3.8%) and epilepsy(3.8%) were recognized as other co morbidities.

All the patients that were discharged with morbidities (n-21) were followed up monthly for further 6 months and was found according to gross motor functional classification systems (GMFCS) only 3 patients had mild to moderate motor disabilities and remaining eighteen patients recovered completely.

There is no large scale data regarding neurological outcome of post COVID infection, Most of the study stated outcome of respiratory symptoms both in children and adults. Most of the study found strikingly low (0.4%) post COVID complications and they found children experienced a resolution of symptoms within 2 weeks of infection, and they recommended additional research to assess neurobehavioral sequelae of SARS-CoV-2 infection in school-aged children[21,22,23,24].

Conclusion:

Neurological involvement of COVID-19 in children is not uncommon, Understanding the pathophysiology of neurologic disease and early initiation of specific management and potential immunological interventions will help to ameliorate both immediate and long term neurological complications of COVID-19.

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