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ORIGINAL ARTICLE

COVID-19 in Children with West Syndrome: An Ambispective Study

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Abstract

Objectives To study the course of West syndrome (WS) and coronavirus disease-19 (COVID-19) in children with WS who contracted SARS-CoV-2 infection.

Methods This ambispective study was conducted at a tertiary-care center in North India between December 2020 and August 2021 after approval from the Institute Ethics Committee. Five children with WS, positive for COVID-19 based on RT-PCR, fulfilled the inclusion criteria.

Results One child with COVID-19 during the first wave was retrospectively included while four children (of the 70 children screened) were prospectively enrolled. The median age at onset of epileptic spasms was 7 mo (2 boys), and that at presentation with COVID-19 was 18.5 mo. Three had underlying acquired structural etiology. Three were in remission following standard therapy, while two had ongoing spasms at the time of COVID-19 illness. During the illness, two of those in remission continued to be in remission while one child had a relapse. The children with ongoing epileptic spasms had variable course [one had persistent spasms and other had transient cessation lasting 3 wk from day 2 of COVID-19 illness, but electroencephalography (on day 8 of COVID-19 illness) continued to show hypsarrhythmia]. Fever was the most typical symptom (and sometimes the only symptom) of COVID-19, with a duration ranging from 1–8 d. Two children had moderate COVID-19 illness requiring hospitalization, while the rest had a mild illness. All the affected children had complete recovery from COVID-19.

Conclusion The severity of COVID-19 illness in children with WS is often mild, while the subsequent course of WS is variable.

Keywords Infantile spasms syndrome · Infantile spasms · Epileptic spasms · Children with epilepsy · Coronavirus disease 2019

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become an inevitable part of our lives. With over 240 million cases and 4.9 million deaths reported across more than 200 countries, the rate of infection and disease severity in children increased during the ongoing second wave of the pandemic in many countries [1]. Although the occurrence of de novo seizures in patients with COVID-19 is well-described, seizure is rarely a presenting feature of COVID-19 [2, 3]. Comorbid COVID-19 in persons with epilepsy (PWE) has been less frequently reported. A recent study revealed that COVID-19 in PWE was not associated with more severe illness. However, seizures as presenting manifestation of COVID-19 were more frequent in PWE (median age 41 y) than in people without epilepsy [4]. While acute symptomatic seizures or worsening epilepsy control in children with epilepsy (CWE) have been less commonly reported with COVID-19, the pandemic has gravely impacted the care of CWE [5, 6]. The occurrence of COVID-19 in a child with pre-existing epilepsy may have varied implications depending on the type of epilepsy or epilepsy syndrome, and ongoing medications.

In this regard, West syndrome (WS) constitutes a distinctive condition considering the peculiar management options (hormonal therapy), need for frequent follow-up, and higher

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risk of severe COVID-19 in infants [7–9]. Unlike other epilepsies, acute febrile illnesses and pyretotherapy (artificial fever therapy) have been associated with spontaneous remission of epileptic spasms and resolution of hypsarrhythmia in children with WS [10]. However, the role of ongoing hormonal therapy in children with WS in modulating COVID-19 severity is debatable [8, 9]. Besides, COVID-19 has been associated with varied new neurological manifestations in children and there are specific concerns for children with neurological disorders [11, 12]. Hence, it is important to understand the implications of COVID-19 in children with WS. The current study provides a glimpse of COVID-19 and WS severity in children with WS who contracted SARS-CoV-2 infection.

Material and Methods

This ambispective study was conducted at a tertiary-care center in North India after approval from the Institute Ethics Committee (vide IEC-10/2020-1798). The study was carried out between December 2020 and August 2021. The primary objective of the study was to collate cases and collect data regarding clinical and laboratory features, treatments, and outcomes in children with WS who develop COVID-19. The secondary objectives included the determination of the disease course of WS and COVID-19.

Children (aged < 24 mo) diagnosed with WS [epileptic spasms with suggestive electroencephalography (EEG), fulfilling the West Delphi consensus criteria], who contracted COVID-19 were enrolled [13]. For the enrolled children, demographic details, age at onset of epileptic spasms, age at initiation of first-line therapy, lead time to treatment (LTTT), etiology, treatment received, response to treatment, number of relapses, etc., were ascertained by retrospective record review and history from parents. Clinical details of COVID-19 [symptoms, results of investigations including COVID-19 RT-PCR, and clinical severity requiring transfer to intensive care unit, mechanical ventilation, progression to septic shock, and COVID-19-related death] were also noted. Comorbidities, comedications, and treatments administered explicitly for COVID-19 were also recorded.

Data were recorded in a Microsoft Excel spreadsheet (Microsoft Office, Microsoft Corp., Seattle, WA, USA). Variables were presented with continuous data as median (interquartile range; IQR) and categorical data as the frequency with percentage. The statistical analysis was done using SPSS 22.0.

Results

Of the seventy children with WS screened for febrile or respiratory illnesses or family history of COVID-19 during the study period, 10 had a febrile illness. Eight of these 10 children underwent COVID-19 RT-PCR and 4 children were positive for COVID-19. One child with COVID-19 during the first wave was retrospectively included while 4 children (of the 70 children screened) were prospectively enrolled after informed consent. Hence, 5 children fulfilled the inclusion criteria and participated in the study.

The median age at onset of epileptic spasms was 7 mo (2 boys) with a median LTTT of 9 wk (Table 1). Three of the 5 children have underlying acquired structural etiology [1 with presumed genetic developmental and epileptic encephalopathy (DEE) and 1 with tuberous sclerosis (TSC)], while all had hypsarrhythmia in pretreatment EEG (Fig. 1). Despite receiving multiple therapies before SARS-CoV-2 infection, 2 had ongoing spasms (1 was gaining developmental milestones while the other had developmental stagnation). During the COVID-19 illness, one of them had no significant change in spasm frequency, while the other had transient cessation of clinical spasms since day 2 of illness lasting for 3 wk (although the EEG continued to show hypsarrhythmia on day 8 of illness). After the transient cessation, there was a recurrence of epileptic spasms with clustering and progressive worsening with developmental stagnation followed by regression.

The other 3 children were spasm-free for a median period of 10 wk before the onset of COVID-19 illness. One of them (the child with TSC) had a relapse with recurrence of spasms during the COVID-19 illness, while the other 2 (underlying etiology: DEE and hypoxic brain injury) continued to be spasm-free till the last follow-up (Fig. 1). The child with relapse responded to a hike in the dose of vigabatrin and has been spasm-free. The child with presumed DEE had transient worsening of movement disorder during the COVID-19 illness, which settled spontaneously by day 5 of illness.

The median age at presentation with COVID-19 was 18.5 mo (range: 13–23 mo; Table 2). Fever was the most typical symptom seen in all children, with a duration ranging from 1–8 d. Two children had moderate disease (possibly with comorbid aspiration pneumonitis) requiring hospitalization. All the affected children had a complete recovery from COVID-19.

Discussion

The present study illustrates the disease course of WS and comorbid COVID-19 in 5 Indian children. With WS comprising nearly 2% of childhood epilepsies and children constituting less than 10% of the COVID-19 cohorts, comorbid WS and COVID-19 are probably rare [14, 15]. Since many children and infants are asymptomatic or mildly symptomatic with upper respiratory symptoms (which are otherwise seen with any viral infection and often settle), the infrequent COVID-19 testing in this age group might be contributory to

Table 1 Baseline characteristics of West syndrome and the impact of COVID-19

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at onset of spasms	4 mo	17 mo	6 mo	13 mo	7 mo
Gender	Female	Male	Male	Female	Female
Lead time to first-line therapy	20 wk	8 wk	12 wk	8 wk	9 wk
Neurological comorbidities	Developmental delay	Developmental delay, evolving cerebral palsy	Developmental delay, movement disorder	Mild autistic symptoms	Developmental delay, evolving cerebral palsy
Etiology	Structural; hypoglycemic brain injury	Structural; hypoxic brain injury	Presumed genetic developmental and epileptic encephalopathy	Tuberous sclerosis	Structural; hypoxic brain injury
Brain MRI findings	Bilateral parieto-occipital gliosis	Bilateral periventricular signal changes, diffuse atrophy	Mild diffuse atrophy	Multiple cortical tubers	Bilateral periventricular signal changes and volume loss
Pretreatment EEG findings	Modified hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Modified hypsarrhythmia
First-line and second-line therapies received	ACTH, VGB, prednisolone, VPA, ZNS, TPM, NTZ	Prednisolone, ACTH, VPA, CLN	VGB, ACTH, VPA	VGB (75 mg/kg/d)	ACTH, VPA, LEV, CLN
First-line therapy to which the child responded	Partly responded to ACTH and VGB combination	ACTH	ACTH	VGB	Initially, responded to ACTH. Subsequently, had relapse which did not respond to prednisolone
Ongoing spasms before COVID-19	Yes; isolated spasms	No; spasm-free for last 10 wk	No; spasm-free for last 4 wk	No; spasm-free for last 12 wk	Yes; clustered spasms
Effect of COVID-19 on spasm frequency	Transient cessation for 3 wk (EEG after 8 d of cessation showed hypsarrhythmia)	No change; had persistent cessation during the COVID-19 illness	No change; had persistent cessation during the COVID-19 illness; no relapse	Relapse with recurrence of clustered spasms after 1 wk of fever	No change; had ongoing spasms as before
Effect of COVID-19 on other neurological symptoms	-	-	Transient worsening of movement disorder (tremulousness, dystonia) lasting 5 d	-	-
Final outcome	Persisting clustered epileptic spasms, with developmental regression	Resolution with persistent cessation + no relapse	Resolution with persistent cessation + no relapse	Spasms responded to increased dose of VGB (100 mg/kg/d) within 3 d	Persisting clustered epileptic spasms, more than > 50% reduction in spasms with VGB (started at discharge)
Last follow-up after COVID-19	12 mo	3 mo	3 mo	3 mo	2 mo 3 wk

ACTH Adrenocorticotrophic hormone, *CLN* Clonazepam, *COVID-19* Coronavirus disease 2019, *EEG* Electroencephalography, *MRI* Magnetic resonance imaging, *NTZ* Nitrazepam, *TPM* Topiramate, *VGB* Vigabatrin, *VPA* Sodium valproate, *ZNS* Zonisamide

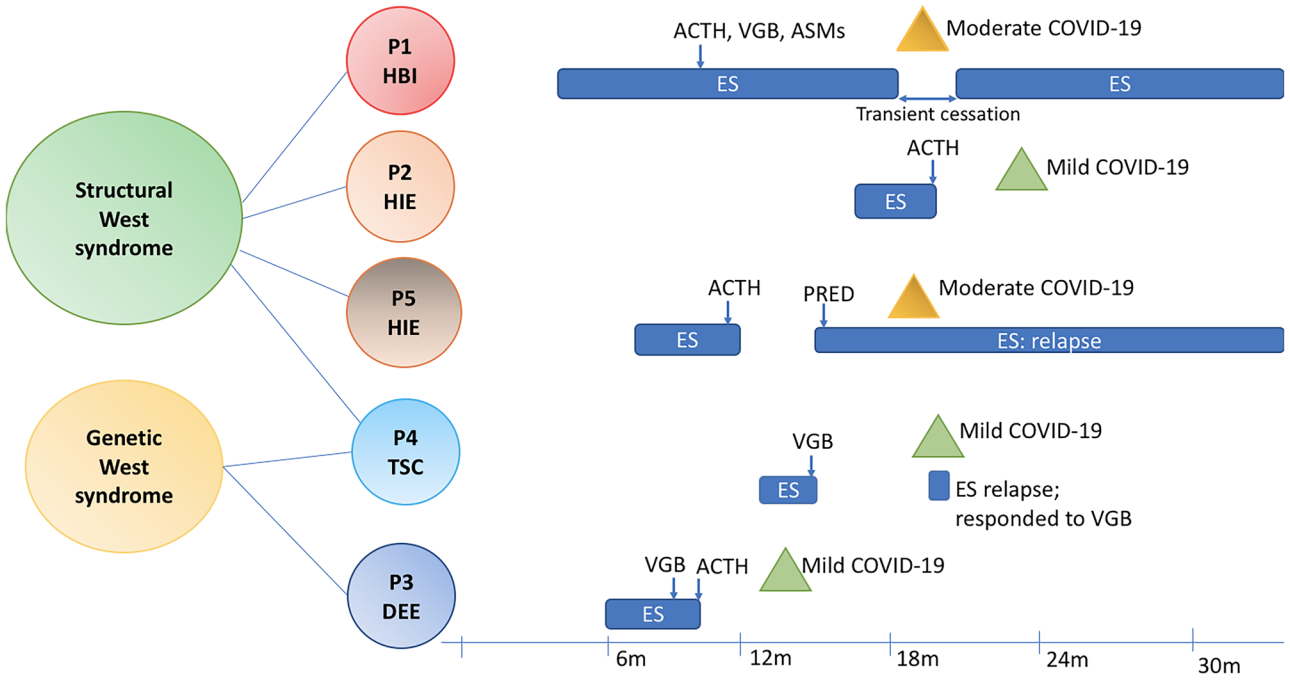

Fig. 1 Diagram representing clinical course in 5 children with West syndrome and coronavirus disease 2019. *ACTH* Adrenocorticotrophic hormone, *COVID-19* Coronavirus disease-19, *DEE* Developmental and epileptic encephalopathy, *ES* Epileptic spasms, *HBI* Hypoglycemic brain injury, *HIE* Hypoxic ischemic encephalopathy, *PRED* Prednisolone, *TSC* Tuberous sclerosis complex, *VGB* Vigabatrin

the lower rate of detection of cases. Under-testing in infants and young children is not just limited to developing countries. As seen in a Spanish study, among 15 children with DEE with typical COVID-19 symptoms, only 7 were tested with RT-PCR [5].

Since the children with WS were being followed-up with teleconsultations during the first COVID-19 wave at the study site (due to several research studies going on in the department), a higher number of children with WS were observed to be infected during the second wave as compared with the first wave (although denominator for the first wave is not available). This goes in hand with the higher number of children infected during the second wave (probably due to vaccination in adults and easing of lockdown restrictions) [16, 17]. Also, for the subsequent surges of COVID-19, it has been contemplated that the children might bear the brunt of the COVID-19 vaccine rollout strategy (older adults followed by young adults and children) due to the unvaccinated status.

Unlike all the previously reported children with DEE or infantile spasms (with genetic or presumed genetic etiology) with COVID-19, 3 of 5 children in the current study had underlying acquired structural etiology [5, 18]. This concurs with a predominance of structural etiology in developing countries [19–21]. Also, the treatment lag (like previous studies) was huge in all 5 children, despite which, 3 had responded and were in remission [19, 22].

Similar to previous reports of SARS-CoV-2 infection in 3 children with DEE and 1 child with cryptogenic WS (in remission), the COVID-19 illness was mild to moderate in the present case series [5, 18]. Although none of the previously reported children with DEE had either seizure or behavioral worsening during the COVID-19 illness, the previously reported child with cryptogenic WS had a relapse after 14 mo of cessation of spasms and was incidentally detected to be COVID positive on screening (asymptomatic for COVID-19) [5, 18]. The disease course in the present study was different, with 1 child having persistent worsening after a transient cessation, 1 child having a relapse (which responded to hike in vigabatrin), while the other 3 had unchanged spasm frequency (2 in remission and 1 with ongoing spasms).

Body temperature plays a critical role in determining seizure threshold and seizure-related brain damage [23]. High-grade fever and febrile illnesses are often known to worsen seizure control (for most convulsive seizure types) by lowering the seizure threshold [23]. In this context, epileptic spasm is a unique seizure semiology where spontaneous resolution has been reported after fever (pyretotherapy) [10, 24]. The possible reasons for this phenomenon include increased plasma concentrations of endogenously secreted adrenocorticotrophic hormone (ACTH) and steroidal hormones in response to stressors, including infections and fever [10].

Table 2 Characteristics of COVID-19 illness in children with West syndrome

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at presentation with COVID-19	18.5 mo	23 mo	13 mo	19 mo	18 mo
Contracted COVID-19 during	1st wave	2nd wave	2nd wave	2nd wave	2nd wave
Ongoing drugs for West syndrome	VPA, ZNS, and NTZ (Off ACTH for last 6 mo)	VPA and CLN (Off ACTH for last 4 wk)	VPA (Off ACTH for last 2 wk)	VGB	VPA, LEV, CLN, and prednisolone
COVID-19 symptom profile					
Fever	Yes; moderate to high grade, lasted 6 d	Yes; moderate to high grade, lasted 2 d	Yes; moderate to high grade, lasted 5 d	Yes; moderate grade fever for 1 d	Yes; high grade for 8 d
Cough	Yes	No	No	No	Yes
Respiratory distress	Tachypnea and noisy breathing, lasted 7 d	No	No	No	Tachypnea and noisy breathing, lasted 10 d
Caregivers affected	No; COVID negative	Fever in mother and sister but both COVID negative	Yes; both parents COVID positive	Yes; both parents COVID positive	No; COVID negative
Need for respiratory support	Yes; low-flow oxygen by nasal prongs; required for 5 d	-	-	-	Yes; nasal CPAP followed by oxygen by nasal prongs; required for 10 d
Other concerns (vasopressor support, renal dysfunction, liver dysfunction)	-	-	-	-	Had compensated shock requiring 1 bolus at admission
COVID-19 severity	Moderate disease (respiratory distress, radiographic evidence of pneumonia)	Mild (not requiring hospitalization)	Mild (not requiring hospitalization)	Mild (not requiring hospitalization)	Moderate disease (respiratory distress, radiographic evidence of pneumonia, compensated shock)
Drugs used for respiratory illness	Amoxicillin+clavulanic acid, oseltamivir	-	-	-	Amoxicillin+clavulanic acid, ceftriaxone
Final outcome of respiratory illness	Complete recovery	Complete recovery	Complete recovery	Complete recovery	Complete recovery

ACTH Adrenocorticotrophic hormone, *CLN* Clonazepam, *COVID-19* Coronavirus disease 2019, *CPAP* Continuous positive airway pressure, *NTZ* Nitrazepam, *VPA* Sodium valproate, *ZNS* Zonisamide

The clinical course and EEG changes following pyretotherapy resemble that following hormonal therapy with clinical cessation reported in most patients by day 4 of fever while hypsarrhythmia resolution occurs by day 6–8 [10]. In the present study, the child with transient cessation of epileptic spasms did not have hypsarrhythmia resolution. EEG could be done only once during illness due to COVID-19–related constraints and resource-limited setting. Following the ACTH therapy initially, she had exhibited > 50% reduction in spasm frequency. The authors believe that the response to pyretotherapy in WS might also depend on the tendency to respond to hormonal therapy in general, LTTT, age at onset, etc. However, the progressive developmental deterioration in this child might be due to subsequent worsening of epileptic encephalopathy. Also, the child with TSC had a brief febrile phase lasting 24 h, and she developed transient relapse after 1 wk of subsidence of fever (due to COVID-19). Duration of fever due to COVID-19 might affect the course of WS in some patients during and after COVID-19 illness.

The current study attempted to describe the implications of SARS-CoV-2 infection in children with WS. With only one previous report of COVID-19 in a child with WS, this case series is a significant addition to the literature. However, due to the few children in the study, it is not easy to draw robust conclusions. Furthermore, due to the pandemic restrictions, EEG changes during the COVID-19 illness could not be studied for children who did not require hospitalization.

Conclusion

Comorbid COVID-19 in children with WS may be underdiagnosed. The severity of COVID-19 illness in children with WS is often mild, while the subsequent course of WS is variable. Proactive COVID-19 testing is desirable in children with WS presenting with fever with or without respiratory symptoms, depending on the regional COVID-19 transmission. Multicenter data would be helpful for further understanding of the repercussions of COVID-19 in children with WS.

Authors' Contributions PM contributed by planning of the study, literature search, patient management, data collection, data analysis, and writing of the manuscript; PD contributed by data collection, data analysis, and critical review of the manuscript for intellectual content; LS, SV, CB, MG, and AS contributed by patient management and critical review of the manuscript for intellectual content; JKS contributed by conception and planning of the study, patient management, data analysis, data interpretation, and writing of the manuscript. All authors approved the final version of manuscript to be published 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. JKS will act as the guarantor for this paper.

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Declarations

Ethical Publication Statement The authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of Interest None.

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