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Navigating Through Guts: A Comparative Study on COVID-19 and Amebiasis in Children

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Abstract

Background and Aims: The coronavirus disease 2019 (COVID-19) has global significance with a notable impact on pediatric populations, exhibiting not only respiratory but also gastrointestinal (GI) symptoms. Given that the prevalence of *Entamoeba histolytica* causing amebiasis in Jordan is 27.8% of annual diarrheal illnesses, our study aimed to delineate the clinical features of COVID-19 in children with a focus on GI manifestations, and to compare these features with those of amebiasis-associated diarrhea.

Materials and Methods: We conducted a retrospective cross-sectional analysis at Jordan University Hospital between September and December 2020. The study cohort included children under 18 years with a confirmed diagnosis of COVID-19, assessed for GI symptoms and compared against age-matched controls hospitalized with diarrhea but negative for COVID-19. We evaluated demographic data, clinical presentations, laboratory findings, and outcomes to differentiate between COVID-19 associated diarrhea (CAD) and amebiasis associated diarrhea (AAD). Results: The study included 229 pediatric patients, with 25 hospitalized cases. Among these hospitalized children, 76% exhibited diarrhea, with 21% having concurrent amebiasis. There was no significant age difference between the CAD and AAD groups. Notably, vomiting and abdominal pain were more prevalent in the CAD group, although this did not translate to longer hospital stays. Furthermore, the incidence rates of amebiasis in COVID-19 positive children did not significantly differ from the control group, indicating no exacerbation of amebiasis by COVID-19.

Conclusions: Our findings suggested that while GI symptoms were prevalent among pediatric COVID-19 cases in Jordan, the clinical course of CAD appears comparable to that of AAD, without increased severity or prolonged hospitalization. However, it is important to note that the study size was small, which may limit the generalizability of our results. This study underscored the importance of considering concurrent etiologies in children presenting with diarrhea during the COVID-19 pandemic and provided a foundational comparative analysis for future research on GI manifestations in pediatric infectious diseases. Further studies with larger sample sizes are needed to validate these findings and explore the full spectrum of GI symptoms in this population.

Keywords: COVID-19, Amebiasis, diarrhea, Children, Jordan.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a highly contagious and pathogenic virus that originated in Wuhan, China in 2019, caused the corona virus disease 19 (COVID-19), and spread globally [1].

To date, it is estimated to have affected over 670 million individuals, with a mortality number reaching 6.8 million [2]. As of the 3rd of October 2023, The United States, India, and France were the countries with the highest infection rate [2]. In Jordan, COVID-19 affected around 1.7 million individuals and the total mortalities reached 14 thousand [3]. Initial reports showed infected children had milder clinical course than adults, but more reports emerged since then about children with severe form of the disease involving multiple organ-systems [4,5].

COVID-19 can range in severity from asymptomatic disease to multiple-organ dysfunction, leading to death with a case fatality rate ranging from 2 to 3% [6]. It is strongly associated with respiratory symptoms during infection, but gastrointestinal (GI) symptoms, such as diarrhea, vomiting, nausea, and abdominal pain, have been identified in subsets of COVID-19 children [7]. In a meta-analysis the pooled prevalence of GI manifestations was 11.5%, and the most frequent GI symptom was diarrhea [8]. The severe form of COVID-19 is referred to by the center of diseases control and prevention multisystem inflammatory (CDC) as syndrome in children (MIS-C) [9]. Other nomenclatures, for the same form, emerged from the World Health Organization (WHO) and the Royal College of Pediatrics and Child Health (UK) [10]. Organ involvement in MIS-C is wide-spread, with the GI system being the most affected in children from the

United States and France [5,11].

A study from Jordan showed GI symptoms were among the most prevalent COVID-19 symptoms in children, and they were present in about 30% of symptomatic hospitalized children with COVID-19 in another study [12,13]. *Entamoeba histolytica* is a common parasitic infection in Jordan, causing amebiasis, and contributing to about 27.8% of annual diarrheal illnesses in Jordan [14]. No studies from Jordan have compared COVID-19 associated diarrhea (CAD) in children with amebiasis associated diarrhea (AAD).

This study aimed to review the clinical characteristics of hospitalized COVID-19 children at a tertiary hospital. Our primary goal was to study the impact of diarrheal illness in COVID-19 children. Our secondary goal was to compare CAD with AAD.

METHODS

This was a retrospective cross-sectional study that was done at Jordan University Hospital (JUH) from September 2020 through December 2020. The study was approved from the institutional review board (IRB) at JUH and the University of Jordan, school of medicine. It included children who were diagnosed with COVID-19, were less than 18 years old, and were followed at JUH. Those children were evaluated either through JUH pediatric clinics; emergency department or during their admission to the hospital. Age-matched controls were used from hospitalized children during the same time period of the study, who were less than 18 years old, had diarrhea illness at the time of the study, and were COVID-19 negative.

A positive case of COVID-19 was defined as a case that had a positive polymerase chain reductase test (PCR) for COVID-19 at JUH. The used kit was e-NAT manufactured by

COPAN Italia. A positive case of CAD in a child was considered when the child was COVID-19 positive, and had a diarrheal illness that was not attributed to other or etiologies. possible pathogens histolytica diarrheal illness, or amebiasis, was defined based on clinical criteria of acute diarrhea, and a positive stool analysis for E. histolytica trophozoite, detected by light microscope. AAD was considered in a child if he/she was COVID-19 negative and had amebiasis. MIS-C case definition required the presence of the following: fever; elevated inflammatory markers; at least two signs of multisystem involvement; evidence of COVID-19 infection; and exclusion of other potential causes. This definition was approved by the WHO and CDC with little differences between them [10]. Controls for the study were selected from children who were hospitalized at the time of the study, had diarrheal illness clinically, had a stool analysis performed at the time of the study and were COVID-19 negative. Children were presumed to have viral induced diarrhea if stool analysis was negative for amebiasis, and there were no concerns for bacterial infection in the clinical setting.

Hospitalized COVID-19 positive children were treated according to JUH – treatment protocol that was adapted from international guidelines [5-7,9-11]. A multidisciplinary team of pediatric subspecialists followed MIS-C patients during and after their hospital

stay. Hospitalized children with amebiasis were treated with oral Metronidazole. Intravenous formulation of Metronidazole was offered at time of oral intolerance.

included: Collected data socio-COVID-19 demographic parameters: infection history and investigations; present signs and symptoms; treatment details; associated co-morbidities; laboratory and radiological studies performed; and length of stay in the hospital. Data was collected from medical records, and were manually entered into excel sheets. These sheets were kept in a hospital computer that was passwordprotected. Statistical Analysis was done using Statistical Package for the Social Sciences (SPSS) software version 20. Two – proportion Z test was used to determine significant differences between proportions of a particular characteristic in two independent groups.

RESULTS

Our study included 229 children who were COVID-19 positive. The majority of the cohort (89%) did not require hospital admission, and were designated "out patients" as shown in figure 1. The majority of hospitalized children (76%) had diarrhea, of whom, 21% had amebiasis. The clinical characteristics of the 229 children are shown in table 1.

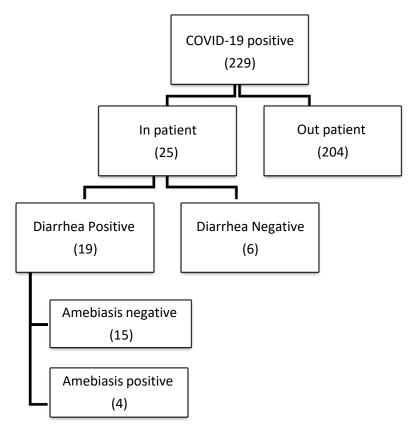


Figure 1: Flow diagram of the study population.

Table 1: The Clinical characteristics of the COVID-19 children (total N=229).

Variable	Frequency	Percentage (%)		
Section one: socio demographic data				
Gender, boys	125	54.6		
Age of the patient (year)	10.9±5.4			
Number of COVID-19 children	Number of COVID-19 children			
Outpatient	204	89.1		
Hospitalized children	25	10.2		
Main cause of patient admission				
GI symptoms	16	64.0		
Respiratory symptoms	7	28.0		
Prolonged fever	2	8.0		
Length of stay in hospital (days)	3.8±2.5			
Duration of symptoms (days)	1.7+-1.4			
Chronic co-morbidities				
Seizure	4	1.7		
Asthma	2	0.9		
Wilson	1	0.4		
IBD*	1	0.4		
Medically free	221	96.5		
Section two: symptoms and signs				
Fever	84	36.7		
Cough	38	16.6		

Variable	Frequency	Percentage (%)
Sore throat	30	13.3
Rhinorrhea	30	13.1
Headache	27	11.8
Decreased activity	26	11.4
Myalgia	24	10.5
Diarrhea	22	9.6
Vomiting	21	9.2
Loss of taste	20	8.7
Insomnia	20	8.7
Nasal congestion	19	8.3
Shortness of breath	15	6.6
Decreased feeding	14	6.1
Abdominal pain	13	5.7
Conjunctivitis	4	1.8
Skin rash	4	1.7
Seizure	3	1.3

^{*}IBD: Inflammatory bowel disease

The majority of children in our cohort (96.5%) did not have chronic or systemic illnesses, and the most prominent presenting symptom was fever (36.7%). GI symptoms (including vomiting, diarrhea, abdominal pain) accounted for about 24.5% of the symptoms. Only six children (2.6%) had MIS-C in this cohort. In comparison to the rest of hospitalized COVID-19 children, MIS-C children were mainly females; had higher ESR; had lower hemoglobin levels; and had longer hospital stay, with p values (0.01, 0.01, 0.02, and 0.02, respectively).

To evaluate the impact of diarrhea presence on hospitalized COVID-19

children, the clinical characteristics of hospitalized COVID-19 children studied based on the presence and absence of diarrhea in table 2. Two-thirds of children (76%) were diarrhea positive, and four of them (21%) were *E. histolytica* positive. Although it was not statistically significant, diarrhea manifested in COVID-19 positive children at a younger age compared to the rest of COVID-19 positive children (p value 0.13). Four cases of MIS-C were found in the COVID-19 - diarrhea positive group in comparison to 2 cases only in the COVID-19 -diarrhea negative group (p value 0.35).

Table 2: The Characteristics of hospitalized COVID-19 children, with and without diarrhea.

Variable	COVID-19 positive – diarrhea positive (N=19)	COVID-19 positive – diarrhea negative (N=6)	p-value
Male Gender	13 (68.4)	3 (50.0)	0.41
Age (year)	6.70 ± 5.40	16.00±0.00	0.13
Vomiting	9 (47.4)	0 (0.0)	0.04
Abdominal pain	5 (26.3)	0 (0.0)	0.2
Decreased activity	5 (26.3)	1 (16.7)	0.63
Signs of dehydration	4 (21.1)	2 (33.3)	0.54
Rhinorrhea	4 (21.1)	0 (0.0)	0.22
Decreased feeding	4 (21.1)	1 (16.7)	0.82

Variable	COVID-19 positive – diarrhea positive (N=19)	COVID-19 positive – diarrhea negative (N=6)	p-value
Cough	3 (15.8)	0 (0.0)	0.3
Seizure	3 (15.8)	0(0.0)	0.3
Nasal congestion	2 (10.5)	0(0.0)	0.41
Fever	10 (52.6)	2 (33.3)	0.41
Sore throat	1 (5.3)	0(0.0)	0.6
Length of hospital stay	4.10±2.60	3.33±2.10	0.54
Hemoglobin	10.97±40.03	11.73 ± 1.90	0.80
CRP	126.91±105.95	144.20±143.52	0.83
WBC	14.70±12.30	15.20 ± 8.20	1.00
ALT	26.00± 7.5	27.2±14.5	1.00
Albumin	3.10±1.00	3.10±0.21	1.00
INR*	2.00±0.90	1.14 ± 0.00	0.42

^{*}INR=international normalized ratio

To evaluate the impact and features of COVID-19 infection on the diarrheal illness, the COVID-19 positive – diarrhea positive group was compared to its age selected control group (COVID-19 negative – diarrhea positive) in table 3. Although vomiting and abdominal pain were more prevalent among COVID-19 positive-

diarrhea positive children (p values 0.02 and 0.00 respectively), the length of hospital stay was shorter in the COVID-19 positive - diarrhea positive group (p value 0.04). Children who were COVID-19 positive had the same incidence of amebiasis as the control group.

Table 3: Clinical characteristics of hospitalized diarrhea children, with and without COVID-19.

Variable	COVID-19 positive – diarrhea positive (N=19)	COVID-19 negative – diarrhea positive (N=48)	p-value
Male Gender	13 (68.4)	26 (54.2)	0.30
Age (year)	6.70±5.40	9.1±6.5	0.82
E. histolytica positive	4 (21.1)	9 (18.8)	1.00
Vomiting	7 (36.9)	6 (12.5)	0.02
Abdominal pain	5 (26.3)	0 (0.0)	0.00
Decreased activity	5 (26.3)	22 (45.8)	0.8
Signs of dehydration	4 (26.3)	11 (22.9)	0.42
Rhinorrhea	4 (21.1)	0 (0.0)	0.00
Decreased feeding	4 (21.1)	0 (0.0)	0.00
Skin rash	3 (15.8)	0 (0.0)	0.01
Nasal congestion	2 (10.5)	0 (0.0)	0.02
Fever	10 (52.6)	21 (43.8)	0.52
Loss of taste	10 (52.6)	9 (18.7)	0.00
Length of stay in hospital	4.10±2.60	4.30±3.14	0.04
ALT	26.00±7.5	16.50±16.90	0.00
Platelets	109.15±111.9	370.8±153.8	0.01

Comparing hospitalized CAD to hospitalized AAD children, vomiting and abdominal pain were more prevalent in the CAD group,

although this did not translate to longer hospital stay (see table 4).

Table 4: Clinical characteristics of hospitalized diarrhea children, with either COVID-19 (CAD) or amebiasis (AAD).

Variable	COVID-19 positive – E. histolytica negative (CAD*) (N=15)	COVID-19 negative – E. histolytica positive (AAD**) (N=9)	p-value
Male gender	11 (73.3)	4 (44.4)	0.20
Age (year)	3.2±1.0	2.4±0.9	0.06
	(Median 2)	(Median 1.5)	
Signs of dehydration	1 (9.1)	2 (22.2)	0.41
Decreased activity	6 (40.0)	5 (55.6)	0.5
Fever	5 (33.3)	4 (44.4)	0.586
Rhinorrhea	4 (26.7)	0 (0.0)	0.1
Vomiting	4 (26.7)	1 (11.1)	0.4
Skin rash	3(20.0)	0 (0.0)	0.2
Decreased feeding	3 (20.0)	0 (0.0)	0.2
Nasal congestion	2 (13.3)	0 (0.0)	0.25
Abdominal pain	2 (13.3)	0 (0.0)	0.3
MIS-C	6 (40.0)	0 (0.0)	0.03
Length of stay in hospital	2.5±1.5	3.0±1.3	0.40

*CAD: COVID-19 associated diarrhea **AAD: amebiasis associated diarrhea

In comparison to the control group who had amebiasis only (n= 9), children with both COVID-19 infection and amebiasis (n=4) had more vomiting and abdominal pain, with p values 0.02 and 0.00 respectively (Table not shown here).

DISCUSSION

To our knowledge, this is the first study to compare COVID-19 associated diarrhea and amebiasis associated diarrhea in children. Several case reports and case series in the adult literature reviewed cases of SARS-CoV-2 and *E. histolytica* co-infection: cases

included amebic liver abscess in some patients; and fulminant colitis in others [15-17]. A systematic review evaluated cases of COVID-19 co-infection with different parasites, including amebiasis, and recommended more attention to such co-infection status [18].

The gastrointestinal tropism of SARS-CoV-2 has been established, but the mechanisms behind digestive symptoms in COVID are still under investigation [19]. It is accepted now that the interaction between SARS-CoV-2 spike S glycoprotein and host receptor proteins, like angiotensin converting

enzyme 2, is the first step in the pathogenesis, but more work is being carried out to explore the successive steps [19]. Such interaction is thought to alter gut microbiome and its inhabitants [19]. By decreasing CD4+ cells and lymphopenia, a study has shown that SARS-CoV-2 infection may activate pre-existing parasitic infections, whereas another study has suggested a protective role of SARS-CoV-2 mediated by gamma interferon production [20,21].

Our study showed the gastrointestinal symptoms to be present in about 24.5% of all children with COVID-19. This is slightly lower than what was previously reported in Jordanian children, but still higher than the pooled prevalence of 11.5% [8,13]. In comparison to a study done in United Arab emirates in 2020, 27% of the children encountered GI symptoms [22]. More studies are needed to verify the accurate prevalence of GI symptoms in COVID children.

The prevalence of amebiasis in our control group was 18.8%. This is lower than the previously reported annual percentage of amebiasis of all diarrheal illness in Jordan (27.8%) [14]. This could be because our study was performed during COVID-19 pandemic. Contact restrictions and social distancing measures during the pandemic could have dropped amebiasis frequency. Similar findings were noticed in other studies [23,24]. A study in Denmark in 2020 compared the number of positive stool samples over a period of time and the effect of social distancing. It showed that the number of positive stool samples decreased significantly during COVID-19 restrictions [23]. Similar results were also found in Cameron regarding positive cases typhoidal salmonellosis and amoebiasis [24].

Our study did not show a difference between the prevalence of amebiasis in the COVID-19 group and the control group (21.1% and 18.8 %, respectively, p value 1.00). This differs from the findings of other studies which have suggested possible protective effect of parasitic infection in COVID-19 patients, with lower incidence and severity of COVID-19 cases associated with parasitic infections [21].

In this study, children with COVID-19 and diarrhea were relatively younger than other children who had COVID-19 only, but this was not statistically significant. Vomiting was more significant in the diarrhea group, but this has not affected any other clinical parameter, including comparable length of hospital stay in both groups. The small sample size might be responsible for not showing potential differences between the two groups.

Other than the presence of MIS-C, which is characteristic for COVID-19, our study did not show any differences that were statistically significant between CAD and AAD. These results may suggest that outcomes from CAD were no worse than AAD. On the other hand, when compared to *E. histolytica* only group, the co-infection with SARS-CoV-2 and *E. histolytica* had more profound symptoms in children, but did not affect length of hospital stay. Further prospective, multi-center, larger studies are needed to support this conclusion.

Our study had a few limitations. The retrospective nature of the study may have affected the reliability of data; similarly the data recording method in medical records may be a limitation. For example, the underreporting of some symptoms, such as the presence or absence of abdominal pain or loss of taste. The small sample size, especially in the subgroup analysis, might have hampered eliciting significant differences, and thus limits generalizability of the study outcomes.

Being a single center study was another limitation. and could interfere generalizability of the results. Due to limited initial resources, and the retrospective nature of the study, no strain analysis was done for COVID-19 cases, and no fecal analysis for other pathogens was performed. Presence of such pathogens can act as a confounding factors in the diarrhea etiology. Long term follow up was not done in our study due to its retrospective design and data availability. This study was done during winter, and this could limit generalizability of data to other

seasons.

In summary, our study provided a valuable insight on the interaction and co-infection between SARS-CoV-2 and *E. histolytica*. Our understanding of the mechanism of COVID-19 injury to the GI tract is still developing, as well as our realization on the consequences of parasitic co-infection. Prospective, multi-center, longitudinal studies are needed in these two venues.

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سبرأغوار الأمعاء: دراسة مقارنة حول كوفيد-19 ومرض الأميبا عند الأطفال

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الملخص

الخلفية والأهداف: لمرض فيروس كورونا 2019 (كوفيد-19) أهمية عالمية وله تأثير ملحوظ على الأطفال، حيث لا تظهر عليهم أعراض الجهاز التنفسي فحسب، بل تظهر أيضًا أعراض الجهاز الهضمي. نظرًا لانتشار جرثومة الأمييا الحاله للانسجه المسببة لمرض الأمييا في الأردن، وتسببها بما نسبته نظرًا لانتشار جرثومة الأمييا الحاله للانسجه المسببة لمرض الأمييا في الأردن، وتسببها بما نسبته لاحديد السمات السريرية لكوفيد-19 لدى الأطفال مع التركيز على مظاهر الجهاز الهضمي، ومقارنة هذه المظاهر مع تلك الخاصة بالإسهال المصاحب بمرض الأمييا.

المواد والطرق: تم اجراء تحليل مقطعي بأثر رجعي في مستشفى الجامعة الأردنية في الفترة ما بين سبتمبر وديسمبر 2020. وشملت مجموعة الدراسة أطفالًا نقل أعمارهم عن 18 عامًا، مع تشخيص مؤكد لمرض كوفيد 19، وتم تقييم أعراض الجهاز الهضمي التي يعانوا منها، ومقارنتها بحالات معياريه متطابقة مع العمر، تم إدخالها إلى المستشفى بسبب الإسهال في نفس وقت الدراسه ولكنها لم تكن تعاني من كوفيد-19. تم عمل تقييم للبيانات الديموغرافية والمظاهر السريرية والنتائج المختبرية للتمييز بين الإسهال المرتبط بكوفيد-19 والإسهال المرتبط بمرض الأميبا.

النتائج: شملت الدراسة 229 مريضاً من الأطفال، مع 25 حالة احتاجت الدخول الى المستشفى. ومن بين هؤلاء الأطفال الذين دخلوا المستشفى، أصيب 76% منهم بالإسهال، بينما أصيب 21% منهم بداء الأميبا المتزامن مع كوفيد 19. لم يكن هناك فرق كبير في العمر بين مجموعات الإسهال المرتبط بكوفيد-19 والإسهال المرتبط بداء الأميبا. والجدير بالذكر أن القيء وآلام البطن كانت أكثر انتشارًا في مجموعة الإسهال المرتبط بكوفيد-19، على الرغم من أن هذا لم يترجم إلى إقامة أطول في المستشفى. علاوة على ذلك، لم تختلف معدلات الإصابة بمرض الأميبا لدى الأطفال المصابين بكوفيد-19 بشكل كبيرعن الحالات المعياريه، مما يشير إلى عدم تفاقم مرض الأميبا بسبب كوفيد-19.

سيرعن الحد والمحتورية المناج التي توصلنا إليها إلى أنه على الرغم من انتشار أعراض الجهاز الهضمي بسبب حويية 17. بين حالات كوفيد-19 لدى الأطفال في الأردن، فإن المسار السريري للاسهال المرتبط بكوفيد-19 يبدو مشابها لمسار الإسهال المرتبط بداء الأميبا، بدون زيادة في خطورة المرض أو الحاجة الى اقامة في المستشفى لفترة أطول. ومع ذلك، من المهم ملاحظة أن حجم الدراسة كان صغيرًا، مما قد يحد من إمكانية تعميم نتائجنا. تؤكد هذه الدراسة على أهمية النظر في المسببات المتزامنة لدى الأطفال الذين يعانون من الإسهال أثناء جائحة كوفيد-19، وتوفر تحليلًا مقارنًا مهما للبحث المستقبلي حول أعراض الجهاز الهضمي في الأمراض المعدية لدى الأطفال. هناك حاجة إلى مزيد من الدراسات بأحجام عينات أكبر للتحقق من صحة هذه النتائج واستكشاف النطاق الكامل لأعراض الجهاز الهضمي لدى هذه الفئة من السكان.

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