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Original Article

Typical and Atypical Clinical Presentation of COVID-19 Infection in Children in The Top of Pandemic in EL-Minia Governorate (Two Center Experience)

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Abstract. ***Background:*** **A novel coronavirus that is identified as the cause of pandemic situation inFebruary2020 and affects adults and children with variable presentation and outcome.**
Objective: **We studied the typical and atypical clinical and laboratory presentation of COVID-19 during the peak of the first wave in two main referral hospitals, upper Egypt EL-Minia governorate.**
Methods: **Among 88 children with suspected cases tested for COVID-19, only 22 proved to be positive. Studied patients were classified into three groups based on age. The first group was 2–5years, the second was 5–10years, and the third included those aged more than 10 years. All patients met diagnostic guidelines established by the Egyptian Ministry of Health.**
Results: **out of the positive 22 (25%) patients, 13(59.1%) of them were male, while 9 (40.9%) were females. All enrolled patients have a history of near contact exposure (100%). Thrombocytopenia was the highest presenting symptom in all enrolled patients18 (81.8%), while other hematological findings were anemia in 11 (50%), thrombotic symptoms in 2 (9.1%), pancytopenia in 2(9.1%) while bleeding was found in 1 patient (4.5%). Fever, present in 16 (72.7%), the most common constitutional symptom in COVID-19, was not reported in all enrolled patients, while sore throat was reported in only 2 patients (9.1%). The respiratory presentation was only dominant in positive chest C.T. finding, 17(72.3%), rather than clinical symptoms; GUT symptoms were the dominant presenting features as vomiting was found in 15 (68.2%), diarrhea in 10 (45.5%), abdominal pain in 11 (50%), jaundice in 9 (40.9%) and dehydration in 6 (27.3%). Neurological symptoms were convulsions in 4 (18.2%), while encephalopathy was 2 (9.1%). Nephritis was the only renal presentation in the enrolled patients, 3 (13.6%). Cardiac presentations were only cyanosis 8 (36.4%) and arrhythmias 6 (27.3%).**
Conclusion: **COVID-19 has many clinical classic presentations in children; however other non-typical presentations like hematological, CNS, and renal presentations have been reported.**

Keywords: COVID-19 infection, Children, EL-Minia governorate.

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Introduction. A novel coronavirus (nCoV) had been recognized as a cause of pneumonia without cause in cases reported from Wuhan, Hubei province, the capital of central China, by the Chinese Center for Disease

Control on January 7, 2020). The newly discovered coronavirus was .defined as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses because its clinical presentation was similar to that of the SARS virus of 2003. The World Health Organization (WHO) in early 2020 renamed the disease as coronavirus 2019 (COVID-19), an acronym of coronavirus 2019. In March 2020, the WHO declared COVID-19 a pandemic.[1,2] The Egyptian Ministry of Health reacted to the pandemic by adopting a standardized country-wide approach and establishing a Scientific Committee for COVID-19. Guidelines and algorithms have been constantly revised as new information has emerged.[3] To date, this observation has not been fully clarified; however, it is now evident that the proportion of affected children with or without symptoms, were much lower than that of adults.[2] Moreover, some infected children presented with severe forms of the disease.[4–6]

At the time of preparation of this work, the number of confirmed cases of covid was approaching 70 million according to WHO with significant mortality and morbidity; it was reported that this disease has diversity in its presentation with typical and atypical clinical manifestations.[7]

To our knowledge, most data of COVID-19 came from adults studied with few reports from children; hence, our aim was to study various aspects of COVID-19 disease, whether typical or atypical, in confirmed cases of COVID-19 in children referred to two major hospitals in EL-Minia governorate, Egypt.

Patients and Methods. Out of 88 children presented with clinical symptoms of suspected COVID-19 infection, clinical data was collected retrospectively from 22 children (2–12 years) who proved to be COVID-19 positive at EL-Minia fever hospital and EL-Minia University Children Hospital in El-Minya governorate between March 1, 2020, and September 30, 2020. All patients met diagnostic guidelines established by the Egyptian Ministry of Health.

All clinical and laboratory data of these children was collected from admission and recruitment hospital data stressing COVID-19 transmission history, specifically: contact exposure, clinical findings, laboratory investigations (blood tests, viral RT-PCR findings), radiological investigations, and full coverage medical examination. Enrolled patients were classified into 3 groups based on age. The first group was 2–5 years, the second was 5–10 years, and the third included those aged more than 10 years. Suspected cases of COVID-19 were transferred from the triage clinic or emergency department to the COVID-19 isolation unit. Patients were subjected to nasopharyngeal swabs for detection of SARS-CoV-2 by (R.T.)-PCR. Patients with respiratory symptoms underwent high-resolution chest-computed tomography followed by a standardized report written by a specialized radiologist. The findings suggestive of COVID-19 are ground-glass opacities, consolidation, bilateral distribution of lesions, round aspect of the lesions, peripheral distribution, and pulmonary embolism.[8,9]

Patients were considered COVID 19 positive infection when fulfilling the following criteria:

(I) a positive SARS-CoV-2 RT-PCR test (sensitivity <60%),[10–12] and (ii) specific aspects of COVID-19 in high-resolution chest C.T. The study was conducted according to the principle of Helsinki and revised and approved by the legal, ethical committee of the faculty of medicine, EL-Minia University. Informed written consent was obtained from patients' caregivers.

Methodology. Nasopharyngeal swabs were collected under strict safety precautions and infection control recommendations. Samples were loaded into viral transport containing tubes, and viral RNA was extracted using the QIAamp DSP Virus Spin Kit, Qiagen, USA. Extracted nucleic acid was mixed with PCR master mix and primers provided commercially by Coronavirus Genesig® Real-Time PCR assay, Genesig UK. Samples were loaded into the Rotor gene thermal cycler from Applied biosystems. After reverse transcription was done at 55°C for 10 minutes, initial denaturation followed for 2 minutes at 95°C, which was followed by 45 cycles each of which was composed of initial denaturation step at 95°C for 10 seconds and annealing and extension step at 60°C for 60 seconds.

Statistical analysis. Data was collected from hospital medical records and analyzed by using the SPSS version 19 program. Numerical data were expressed as median and range values, and non-numerical data were expressed as numbers and frequencies. Tables and figures were formulated by using the Excel program.

Results. The proved positive COVID 19 patients out of 88 suspected cases were 22 (25%). Thirteen (59.1%) of them were male, while 9 (40.9%) were females. Patients were classified into 3 groups: the first one was patients 3-5 years and enrolled 3 patients (13.6%), the second group enrolled 18 patients (81.8%) who were 5-10 years and the last group enrolled 2 (9.1%) patients.

All enrolled patients have history of near contact exposure (100%). Thrombocytopenia was the highest presenting symptom in all enrolled patients,18 (81.8%), while other hematological findings were anemia in 11 (50%), thrombotic symptoms in 2 (9.1%), pancytopenia in 2 (9.1%), while bleeding was found in 1 patient (4.5%). Fever, the common constitutional symptom in COVID-19, was present in 16 (72.7%), so, it was not reported in all enrolled patients, while sore throat was reported in

only 2 patients (9.1%). The respiratory presentation was dominant in positive chest C.T. finding, 17(72.3%), rather than clinical symptoms. GUT symptoms were the dominant presenting feature as vomiting was found in 15 (68.2%), diarrhea in 10 (45.5%), abdominal pain in 11 (50%), jaundice in 9 (40.9%), and dehydration in 6 (27.3%). Neurological symptoms were convulsions in 4(18.2%), while encephalopathy was 2(9.1%). Nephritis was the only renal presentation in the enrolled patients3 (13.6%). Cardiac presentations were only cyanosis 8 (36.4%) and arrhythmias 6 (27.3%) **(Table 1, figure 1).**

The highest group of patients was above the age of 10 years (median=11). Serum ferritin and LDH level were the highest in the age group 2-5 years (median= 2000 for both). Serum CRP was highest in the age group above 10 years (median=85). D-dimer was highest at the age 2-5 years (median=1) **(Table 2, figure 2).**

Discussion. In this study, screening patients with clinical symptoms enrolled 88 children. Of them, 22 proved to be COVID-19 positive (25%); all were positive for contact exposure indicating that direct exposure is the most important factor in contracting the disease in children. In many previous publications, cough and fever are the most frequent symptoms in children.[13–18]

Most SARS-COVID-19 symptoms were attributed in recent literature to a multi-system inflammatory syndrome in children (MIS-C). Common clinical features of MIS-C include fever, mucocutaneous presentations (rash, conjunctivitis, edema of the hands/feet, red/cracked lips, and strawberry tongue), myocardial dysfunction, cardiac conduction abnormalities, shock, gastrointestinal symptoms, and lymphadenopathy. There are also increasing reports of neurologic involvement in select patients, manifesting as severe headaches, altered mental status, cranial nerve palsies, or meningismus. However, these findings are nonspecific and can also occur in other types of infections and in non–infection-related conditions.[19]

While fever is the gold standard sign in COVID-19 infection, only 16 (72%) of our patients presented with fever. A recent systematic publication reported the same

Table 1. Frequency of different presenting clinical data at different age groups.

	Total	2-5 years (n=3)	5-10 Years (n=18)	>10 years (n=2)
Age (N/%)	22 (100)%	3 (13.6%)	18 (81.8%)	2 (9.1%)
Male	13(59.1%)	2(9.1%)	10(45.5%)	1(4.5%)
Female	9 (40.9%)	1 (4.5%)	8 (36.4%)	0 (0%)
Fever	16 (72.7%)	1(4.5%)	13(59.1%)	2 (9.1%)
Contact exposure	22 (100%)	1 (4.5%)	18 (81.8%)	3 (13.6%)
Sore throat	2 (9.1%)	0 (0%)	2 (9.1%)	0 (0%)
Dyspnea	5 (22.7%)	0 (0%)	5 (22.7%)	0 (0%)
Anosmia	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fatigue/asthenia	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Positive CT findings	17(72.3%)	3 (13.6%)	12 (54.6)	2(9.1%)
Vomiting	15 (68.2%)	1 (4.5%)	11 (50%)	3 (13.6%)
Diarrhea	10 (45.5%)	1 (4.5%)	8 (36.4%)	1 (4.5%)
Dehydration	6 (27.3%)	1 (4.5%)	4(18.2%)	1 (4.5%)
Abdominal pain	11 (50%)	1 (4.5%)	8 (36.4%)	2 (9.1%)
Jaundice	9 (40.9%)	0 (0%)	9 (40.9%)	1 (4.5%)
Hepatomegaly	1 (4.5%)	0 (0%)	1 (4.5%)	0 (0%)
Encephalopathy	2(9.1%)	0 (0%)	2(9.1%)	0 (0%)
Convulsions	4(18.2%)	0 (0%)	3 (13.6%)	1 (4.5%)
Anemia	11 (50%)	1 (4.5%)	9 (40.9%)	1 (4.5%)
Thrombocytopenia	18(81.8%)	1 (4.5%)	15 (68.2%)	2(9.1%)
Lymphopenia	7 (31.8%)	1 (4.5%)	5 (22.7%)	1 (4.5%)
Bleeding symptoms	1 (4.5%)	0 (0%)	0 (0%)	1 (4.5%)
Thrombotic symptoms	2(9.1%)	0 (0%)	1 (4.5%)	1 (4.5%)
Pancytopenia	2(9.1%)	0 (0%)	1 (4.5%)	1 (4.5%)
Nephritis	3 (13.6%)	0 (0%)	3 (13.6%)	0 (0%)
Dysrhythmia	6 (27.3%)	0 (0%)	6 (27.3%)	0 (0%)
Cyanosis	8 (36.4%)	0 (0%)	7 (31.8%)	1 (4.5%)
PCR	22(100%)	2 (9.1%)	18(81.8%)	2 (9.1%)

Table 2. Some laboratory data of studied patients.

Parameter	Total	2-5 years	5-10 years	More than 10 years
Age (median)	7	2	7	11
Serum ferritin (median)	1619	2000	1589	1667
LDH (median)	1147.1	2000	1122.9	1007.3
CRP (median)	55.3	24	51.9	85.3
D Dimer (median)	0.82	1.0	0.83	0.0.67

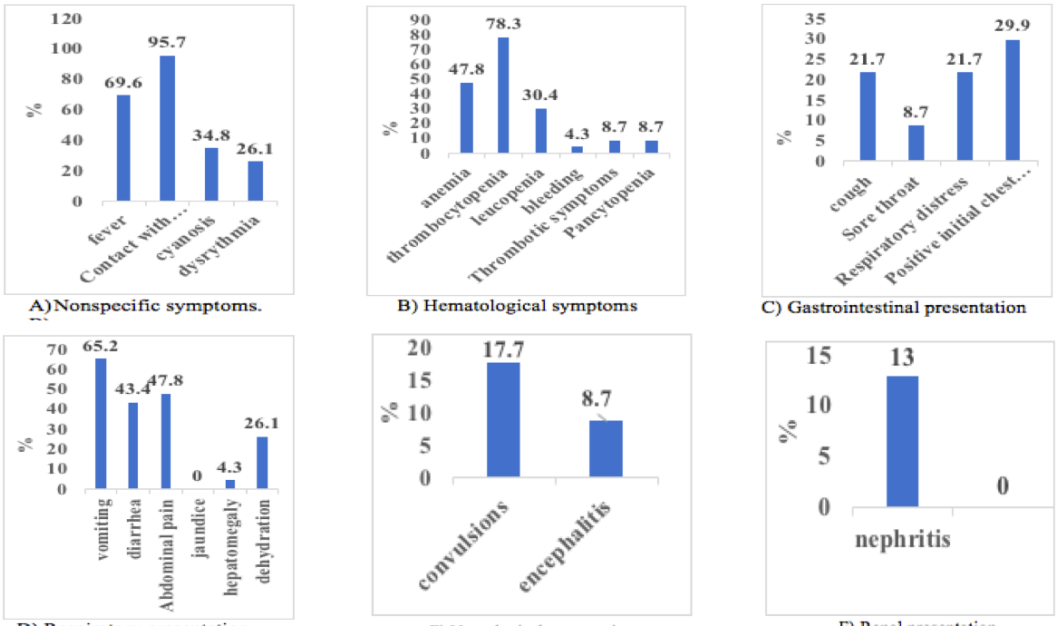

Figure 1. Frequency of different systemic clinical presentations of the studied patients.

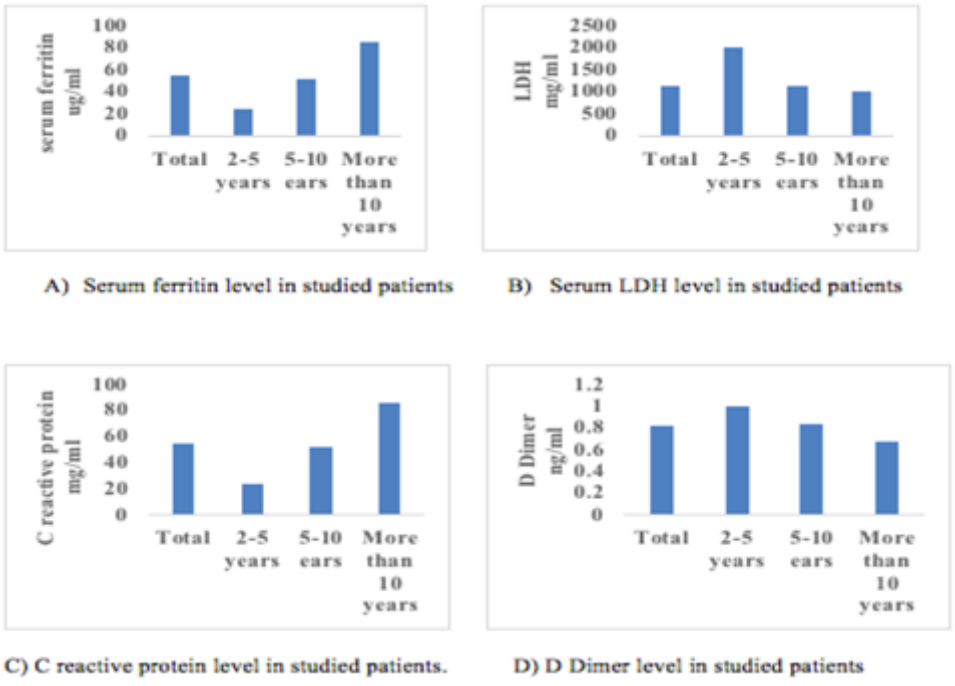

Figure 2. Laboratory data of the groups of affected patients.

results in asymptomatic SARS-COVID infected children.[10,20] while another study suggested that nearly half of pediatric COVID-19 infections are mostly asymptomatic.[21] The nonspecific signs of infection, characteristic of COVID-19 in adults, bone pain, loss of smell, and taste sensation, could not be demonstrated in the enrolled patients. The detection of such symptoms in children is challenging. These are subjective symptoms that could not be expressed -if present- in children. Moreover, these symptoms are nonspecific and could be manifested in some infectious and non-infectious conditions such as influenza and allergic rhinitis. Regarding the respiratory presentation in the studied patients, most respiratory symptoms known are not dominant, but the only dominant clue for respiratory affection was the positive radiological findings (72.3%). A wide diversity of respiratory presentations is common in COVID-19 started with a cough and sore throat until severe respiratory symptoms may mandate mechanical ventilation. Children have significantly lower hospitalization rates than adults, suggesting that children have less severe COVID-19 illness.[22-24]

Gastrointestinal presentation in our patients under study was evidenced by a large percentage of symptoms, including vomiting, diarrhea, abdominal pain, jaundice, and hepatomegaly. The liver and gastrointestinal tract could be the target sites for COVID-19 infection in children.[24,25] This preference can be explained by greater expression of the angiotensin-converting enzyme 2 (ACE2), the major receptor of the SARS-CoV-2 virus in the liver and intestinal tract. It was also postulated that SARS-CoV-2 viral RNA had been detected in patients in many recent previous reports suggesting that the role of the fecal-oral route of COVID-19 transmission can explain the higher percentage of gastrointestinal manifestations in our study.[21,24,25]

Several mechanisms could explain hepatic involvement in patients with COVID-19, including direct viral invasion of liver cells, systemic inflammation, and drug toxicity, as evidenced by autopsy findings that showed portal mild lobular injury and moderate microvascular steatosis.[24-26]

When talking about neurological signs, encephalopathy and convulsions were present in our patients, mainly of the younger age group. Neurological manifestations may be attributed to a febrile illness or to viral CNS invasion because the virus binds to the human ACE-2 receptors found in the cerebral vascular endothelium.[27,28] Coagulopathy and subsequent infarction could be another possible mechanism.[29-31]

A wide variety of hematological signs (anemia, bleeding, thrombotic events) and laboratory findings (thrombocytopenia, lymphopenia, elevated D Dimer) were found in groups under study.[32-34] Lymphopenia was found in 7% of enrolled patients; the underexpression of ACE2 receptor on lymphocytes in children could explain the infrequent occurrence of lymphopenia in children with subsequent better prognosis.[33,35,36] We suggest that lymphopenia rarity in the immature immune system of the younger age group causes lower reaction to COVID-19 infection than adults.

Anemia, the commonest hematological finding of the enrolled patients, could be immune-mediated or of the inflammatory base due to multi-system inflammatory syndrome.[33-38] It may also be explained by bleeding or frequent blood sampling.

The pathophysiology of COVID-19-induced coagulopathy is unclear to date. The complement system overactivation may be a factor of thrombotic events in COVID-19 infection.[29,39] The extracellular COVID-19 RNA has a dual effect on the coagulation system pathway. One of them acts as a natural factor VII-activating protease cofactor,[29,40] and the other increases the autoactivation of proteases of the intrinsic pathway, such as factors XII and XI.[29,41] Also, it has been reported that antiphospholipid antibodies may play a role in COVID-19-associated thrombosis.[30,32,34] COVID-19 may cause disseminated intravascular coagulation in adult patients, with a mild decrease in platelet count and mild prolongation of partial thromboplastin time, but no signs of microangiopathy.[29]

Three cases of the patients under study were presented with nephritis. No previous studies could explain the cause of nephritis in COVID-19 infection. It could be due to complement activation and consumption[40] or maybe secondary to active thrombotic process.[29] Another explanation is an inflammatory cause as a part of the systemic inflammatory response.[42-46]

Arrhythmia found in 27.3% of patients could be linked to fever and acute viral myocarditis. It may also be associated with electrolytes disturbances induced by acute gastroenteritis or syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by severe respiratory or systemic inflammatory illness.[47] Cyanosis, found in 36.4% of patients, could be due to respiratory decompensation, hypovolemic shock, or heart failure.[48-53]

Regarding the age distribution, most cases (81.8%) were at 5–10 years of age. Younger children are not at higher risk of COVID-19 illness.[41-45] however no available data about the rarity of this disease in early childhood. The large scale of pediatrics at different age groups is needed to clarify this discrepancy in COVID-19 illness in different pediatric age groups.

Limitation of the study. There are some limitations to our study. The first one is the limited sample size which was the major concern; the second limitation was the overlap between the COVID 19 symptoms and other multiple systems disorders. This means that much more COVID 19 children are underestimated. Finally, there is evidence that COVID-19-related multisystemic inflammatory syndrome could be a complication in the disease spectrum.

Conclusions. COVID 19 infection could present in children with multi-system disorders with a higher frequency than in middle childhood. The overlap between COVID 19 symptoms and other systemic disorders could share in the underdiagnosis of a large population.

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