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Severe Malnutrition and Anemia Are Associated with Severe COVID in Infants

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ABSTRACT

Background: COVID-19 is uncommon and less severe in children than adults. It is thought that infants may be at higher risk for severe disease than older children. There is a paucity of literature on infants with COVID, particularly those with severe disease.
Objective: We describe demographic, epidemiologic, clinical, radiological, laboratory features and outcomes of infants with confirmed SARS-CoV-2 infection admitted to a tertiary care teaching hospital in Pune, India
Methodology: Infants who tested positive for SARS-CoV-2 and were admitted between 1 April 2020 and 7 August 2020 were included in the study.
Results: A total of 13 infants were admitted during the study period. The median age was 8 months (IQR 6) and nine were male. Common presenting features were fever ($n = 8$, 62%), poor feeding, irritability, and runny nose ($n = 3$, 23%). Comorbidities noted were severe acute malnutrition (SAM) in three cases (23%) and nutritional megaloblastic anemia, iron deficiency anemia, sickle thalassemia and renal calculi in one case (8%) each. There was a history of low birth weight in two cases (15%). Pallor was noted in three cases (23%), SAM in three cases (23%) and tachypnea and respiratory distress in four cases (30%). Severe anemia, thrombocytopenia, elevated ferritin, abnormal procalcitonin, abnormal C Reactive Protein and deranged D-dimer was noted in three cases (23%) each. Neutrophil–lymphocyte ratio was normal in all cases. Three infants (43%) had evidence of pneumonia on the chest radiograph, of which one had adult respiratory distress syndrome (ARDS) like pattern, one infant had cardiomegaly and perihilar infiltrates. Hydroxychloroquine and azithromycin were given to five patients (38%), Intravenous Immunoglobulin and

methylprednisolone were administered to one patient (8%). One infant died of ARDS with multi-organ dysfunction with refractory shock and hemophagocytic lymphohistiocytosis.
Conclusion: SAM and anemia may be associated with severe COVID in infants.

KEYWORDS: infant, COVID, severe malnutrition, anemia

INTRODUCTION

On 11 March 2020, COVID-19 was pronounced as a pandemic by the World Health Organization. While all age groups are at risk, individuals with comorbidities and the elderly are more likely to have severe disease and poor outcomes. Children seem to have less severe clinical symptoms when infected [1]. In the largest pediatric population-based study to date with 2143 cases, over 90% ranged from asymptomatic to moderate. However, the proportion of severe and critical cases was 10.6% under 1 year of age, when compared with 7.3%, 4.2%, 4.1% and 3.0% among the 1–5, 6–10, 11–15 and >15-year subsets, suggesting that infants may be at higher risk of severe respiratory disease than previously thought [2]. Studies from Europe have shown that the majority of infants have mild disease, however, infants with comorbidities may have a higher risk of severe disease [3, 4]. Even so, there is limited data on clinical presentation and outcome of COVID-19 in infants, particularly from developing countries. Our case series provides important data on epidemiology, clinical presentation, radiology, laboratory findings and outcomes in this at-risk population.

METHODS

The study site was Sassoon General Hospital, a tertiary care hospital affiliated to B.J. Government Medical College, Pune, India. For this retrospective study, we identified all hospitalized infants diagnosed with COVID-19 infection between 1 April 2020 and 7 August 2020. One 13-month-old child was included in the study as this was the only fatal case which authors felt would make a significant contribution to the knowledge of severe COVID in young children. Data were obtained from medical case records and interviews with family members of admitted infants.

The following variables were collected: demographic information, including age, sex and geographic location, family clustering (≥1 infected family member residing with the infant), presenting symptoms, duration of symptoms before presentation, comorbidities, the severity of the disease, laboratory parameters, chest radiograph findings, administered antiviral and antimicrobial therapies, duration of hospital stay and outcomes.

The following investigations were done on all admitted infants: Chest radiograph, hemogram, kidney/hepatic function, C-reactive protein, procalcitonin, ferritin, D-dimer, LDH, CPK-MB, PT INR and APTT. Serum amylase, vitamin B_{12} and vitamin D were done in selected patients.

Nasopharyngeal swabs were collected during hospitalization. All testing was conducted at the Sassoon General Hospital Laboratory using a real-time reverse transcriptase-polymerase chain reaction assay (Abbott systems M 2000SP and M 2000 RT). This study was approved by the institutional ethics committee of B.J. Government Medical College.

RESULTS

Thirteen SARS-CoV-2 infected infants were identified between 1 April 2020 and 7 August 2020. All infants were hospitalized, nine were male. The youngest was aged 3 and the oldest was 13 months. The median age was 8 months (IQR 6). Eleven infants were from Pune Municipal Corporation limits, while two were from rural areas of Pune district.

Table 1 describes in detail the epidemiology and clinical characteristics of the 13 infants. Four infants were asymptomatic but tested positive for COVID-19 as a part of contact screening. The median time to admission from the development of symptoms was 2 days (IQR 1), and between admissions to diagnosis was 12 h (IQR 3). Even though 4 of the 13 infants had tachypnea and respiratory distress on admission, their pulse oximeter saturation on admission was more than 94% in room air.

Families of nine infants had at least one infected family member, with the infant's infection occurring after the family members' infection. However, in four

TABLE 1 *Epidemiology and clinical characteristics of thirteen COVID-19 cases in infants*

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Gender (M/F)	Female	Male	Male	Male	Male	Male	Male
Age (months)	13	9	3	4	9	7	6
Contact	No	No	Yes (father)	Yes (grandfather)	No	Grandfather, father (HCW), mother	Father, mother
Presenting symptoms	Fever 2 days, poor feeding (14 days), irritability 2 days	Fever 2 days, irritability, poor feeding	Fever 1 day	No	Fever 4 days, vomiting (2 days), melena (2 days), breathlessness (1 day), poor feeding	Fever 2 days, irritability (2 days)	Fever 2 days, running nose (2 days)
Days from illness onset to admission	2	2	1	NA	4	2	2
Co-morbidity	SAM, severe megaloblastic anemia	Severe nutritional rickets, spiral fracture of left femur	No	No	Sickle-thalassemia	Sever acute malnutrition, bilateral renal calculi, suspected renal tubular acidosis	Late preterm, NICU stay of 10 days (for respiratory distress and jaundice, was not ventilated), low birth weight (2.15 kg)
Complications	Thrombocytopenia, direct hyperbilirubinemia, anemia ARDS, shock encephalopathy, hemophagocytic lymphohistiocytosis	Severe thrombocytopenia, anemia	Direct hyperbilirubenemia	No	Severe anemia, thrombocytopenia	Possible Severe bacterial infection	No
Non-invasive ventilation	Yes	Yes (HHFNC)	No	No	Yes	Yes	No
Invasive ventilation	Yes	No	No	No	No	No	No
Methylprednisolone	Yes	No	No	No	No	No	No
Intravenous Immunoglobulin	Yes	No	No	No	No	No	No
Hydroxychloroquin/ azithromycin	Yes	Yes	No	No	Yes	Yes	No
Length of stay (days)	6	12	7	10	13	14	14
Outcome	Died	Discharged (D10 swab negative)	Discharged (D5 swab negative) Hyperbilribunemia resolved	Discharged (D10 swab negative)	Discharged (D10swab negative)	Discharged (D10 swab negative)	Discharged (D10 swab negative)
Other drugs	Enoxaparin, vitamin B12, PRBC, Meropenem, Vancomycin, supplements	Cholechalciferol, Ceftriaxone, supplements, PRBC	Supplements	Supplements	Meropenem, Vancomycin, PRBC, supplements	Sodium bicarbonate (oral) Piperacillin-Tazobactam, supplements	Ceftriaxone, supplements

Table 1. Continued

	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13
Gender (M/F)	Male	Female	Female	Male	Male	Female
Age (months)	3	11	8	4	11	8
Contact	Father	No	Grandmother	Grandmother	Grandmother	Mother, father
Presenting symptoms	No	Fever 2 days, seizures (hypocalcemic)	No	No	Running nose 2 days	Fever 3 days, runny nose 3 days
Days from illness onset to admission	NA	3	NA	NA	2	3
Co-morbidity	low birth weight, failure to thrive due to poor nutrition	No	No	No	No	Anemia (iron deficiency)
Complications	No	No	No	No	No	No
Non-invasive ventilation	No	No	No	No	No	No
Invasive ventilation	No	No	No	No	No	No
Methylprednisolone	No	No	No	No	No	No
Intravenous Immunoglobulin	No	No	No	No	No	No
Hydroxychloroquin/azithromycin	No	No	No	No	No	Yes
Length of stay (days)	14	10	8	8	3	7
Outcome	Discharged (D10 swab negative)	Discharge (D10 swab negative)	Discharged(D5 swab negative)	Discharged (D5 swab negative)	Discharge on request (D5 swab negative)	Discharged (D5 swab negative)
Other drugs	Supplements	Ceftriaxone, supplements, IV Calcium gluconate	Supplements	Supplements	Supplements	Supplements

cases, there was neither history of contact with the COVID case, nor any of the family members tested positive. Three of the infants required care in a high dependency unit while one infant developed severe adult respiratory distress syndrome (ARDS), hemophagocytic lymphohistiocytosis, and multi organ dysfunction syndrome and required mechanical ventilation.

Laboratory abnormalities commonly noted were anemia, thrombocytopenia, elevated CRP and ferritin (Table 2). Notably, serum ferritin was highly elevated in the infant who died.

Radiological findings seen in our study were bilateral patchy consolidation in middle and lower zones in two cases, cardiomegaly with perihilar infiltrates and ARDS pattern in one case each. In nine infants, the chest radiograph was normal. We could not do a CT chest in any of the cases due to the unavailability of the CT machine in the designated COVID building.

DISCUSSION

Our study focuses exclusively on infants with COVID and reports severe COVID disease in four of the seven infants. All four infants who had severe disease, including the infant who died, had comorbidities.

It is known that COVID-19 is less common in children including infants. This may be due to a lower risk of exposure or incomplete identification due to mild or asymptomatic disease, rather than resistance to infection [5]. Parri *et al.* [3] have reported 40 out of 100 children studied were infants, there was no mortality in this study. However, Götzinger *et al.* [4] in their series of 582 children and adolescents had 230 children (40%) below 2 years of age with a high proportion of ICU admissions (48%) in this age group. Feld *et al.* [6] have described COVID in three infants below two months of age.

Nine of the thirteen infants were male. Previous studies have also shown higher percentages of infection and severe disease in men than women [7]. This may partly be due to less susceptibility of females to COVID. However, gender inequality and poor health-seeking behavior for girls in India may also be a contributing factor.

Family clustering occurred for 9 of the 13 infected infants. Infants who have infected family members should be closely monitored for the development of symptoms and identified early to ensure timely management.

Fever and irritability were common symptoms in our series. In a series of three infants, Feld *et al.* [6] reported lethargy as a feature, none of our cases showed lethargy. This could be because the infants in our case series were slightly older when compared with infants described by Feld et al. Earlier studies on infants with COVID have described mild disease and good outcomes [5]. In the review from Wuhan Children's Hospital, the authors describe the death of a 10-month-old child with intussusception who developed multi-organ failure and died 4 weeks after admission [8]. Cui *et al.* [9] described a 55-day-old otherwise healthy girl presenting with rhinorrhea and cough, with known SARS-CoV-2 exposure, who was admitted, tested positive and subsequently developed liver and cardiac injury. In both cases, the infants did not have any comorbidity. Our study suggests that severe disease is not uncommon in infants, particularly in those with risk factors of severe malnutrition and severe anemia.

Nine of our cases had comorbidities, of which four developed severe disease. Shekerdemian *et al.* [10] reported a high prevalence of comorbidities amongst children with COVID admitted to US and Canadian Pediatric Intensive Care Units with medically complex disease, immunosuppression and obesity as a risk factor for severe disease. The risk factors described in our series in contrast were severe acute malnutrition (SAM) and severe anemia. This difference may be explained by the fact that India still has a huge burden of severe malnutrition and anemia in children when compared with the developed world. The only mortality in our case series occurred in a severely malnourished child who also had severe megaloblastic anemia [11].

The laboratory abnormalities described in our series are consistent with those described in adults with severe disease except for two notable abnormalities-direct hyperbilirubinemia which was seen in four cases and normal neutrophil–lymphocyte ratio (NLR) in all cases. While there is some evidence of higher bilirubin levels in patients with more severe

Table 2. Laboratory and chest radiography findings of the thirteen COVID positive cases in infants

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13
Hemoglobin(gm/dl)	2.2	6.9	11.1	9.6	3.1	9.6	10.2	9.7	5.1	9.5	8.6	10.2	7.4
White blood cell count (x 10^9/l)	13	12	13	9	16	20.8	9.1	6.32	2.4	9.9	10.1	10	7.6
Neutrophil count (x 10^9/l)	2.5	7.9	2.9	3.5	6.0	3.2	2.6	3.4	1.2	1.1	1.1	2.2	1.4
Lymphocyte count (x 10^9/l)	8.7	2.8	9.6	4.4	5.7	3.1	5.3	2.2	1.1	8.0	8.1	7.1	5.7
Platelet count (x 10^9/l)	105	10	255	266	188	487	283	331	203	352	177	304	491
Neutrophil: lymphocyte ratio	0.28	2.8	0.3	0.79	1.05	1.03	0.49	1.54	1.09	0.13	0.13	0.3	0.24
Urine analysis	Normal	Normal	Normal	Normal	Normal	10–15 pus cells/hpf	Normal	Normal	Normal	Normal	Normal	Normal	Normal
CRP (mg/dl)	2.8	Negative	Negative	Negative	Negative	4.2	Negative	Negative	1.8	Negative	Negative	Negative	Negative
Procalcitonin (ng/ml)	1.6	15.4	0.04	0.02	0.27	14.5	0.2	0.1	4.5	0.03	0.29	0.06	0.1
Serum ferritin (ng/dl)	1976	166	115	24	64	85	54	NA	25	25	25	47.59	2.14
Serum albumin (gm/l)	3.6	4.4	4.2	4.3	4.6	4.4	4.3	4.1	4.4	4.4	4.5	4.6	4.2
Serum bilirubin (total/direct) (mg/dl)	2.1/1.7	0.7/0.5	2.8/1.37	0.7/0.6	3.8/1.7	0.4/0.3	0.58/0.2	0.99/0.4	1.15/0.5	2.23/1.13	1.14/0.5	0.2/0.1	0.6/0.14
Serum ALT (IU/l)	20	67	81	60	52	46	59	27	25	14	14.6	18	65
Serum AST (IU/l)	51	37	39	51	92	22	40	54	88	49	45	38	21
BUN (mg/dl)	53	41	14	24	53	58	25	38	43	18	27	22	29
Serum creatinine (mg/dl)	1	0.6	0.3	0.5	0.7	0.5	0.4	0.5	0.6	0.4	0.5	0.7	0.5
Serum sodium (mEq/dl)	146	130	127	141	145	142	133	133.4	119	134	132	138	139
Serum potassium (mEq/dl)	5.1	4.6	4.3	4.3	3.5	5.2	3.95	3.83	3.09	4.3	4.5	4.21	4.4
Serum calcium (mg/dl)	8.9	8.2	8.8	9.1	9.0	9.1	8.6	9.2	7.7	9.1	8.9	9.3	10.5
Serum phosphorous (mg/dl)	3.6	2.8	4.0	3.8	4.7	4.2	3.9	4.0	2.9	4.2	4.1	3.9	4.0
Serum Alk.Phos (U/l)	252	864	286	216	170	324	226	255	946	344	581	207	177
LDH (U/l)	ND	529	577	ND	ND	760	230	ND	773	642	629	ND	639
CPK-MB (IU/l)	37	51	55	ND	8	105	10	47	89	65	63	23	24
PT IN	2.1	1.2	1.1	ND	1.18	1.3	1.0	1.04	1.65	1.02	1.06	1.2	1.1
APTT (s)	36.8	46.8	32.7	ND	39.7	40	34.8	40.4	52	32	ND	42	37
D Dimer (mg/l)	8.5	6.9	0.6	ND	0.2	2.5	0.3	0.33	2.35	1.7	0.7	0.3	0.82
Serum amylase (U/l)	8.2	26	20	ND	ND	17	39	90	35	12	6	92	24
Vitamin B12 (pg/ml)	50	56	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Vitamin D (25 OHD) (ng/ml)	ND	10	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	34
Dengue/rapid malaria test	ND	Negative	ND	ND	ND	50	ND	0ND	ND	ND	ND	ND	ND
Urinary Ca/Cr ratio	ND	ND	ND	ND	ND	Normal	ND	ND	ND	ND	ND	ND	ND
Chest radiograph	ARDS	Bilateral patchy consolidation in mid and lower zone	Normal	Normal	Cardiomegaly Perihilar infiltrates	Bilateral patchy consolidation in Mid and lower zone	Normal	Normal	Normal	Normal	Normal	Normal	Normal

CRP, C reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; CPK-MB, creatine-phosphokinase myocardial band; PT-INR, prothrombin time-international normalized ration; APTT, activated partial thromboplastin time; Serum Alk.Phos., serum alkaline phosphatase; urinary Ca/Cr ratio, urinary calcium creatinine ratio; ND, not done.

COVID disease, this evidence is primarily from adult studies [12]. Chai *et al.* [13] confirmed that healthy liver tissue does have ACE2 receptor expression, and the ACE2 receptor of bile duct epithelial cells is 20 times that of hepatocytes. Therefore, it is speculated that the new coronavirus can enter bile duct epithelial cells through the ACE2 receptor to cause liver damage.

A study by Wu *et al.* [14] suggested that NLR may not be useful as a predictor of severe disease in children, but they did not specifically analyze data on infants. Our study suggests that NLR may not be useful as a marker of severe disease in infants.

The limitation of our study includes small sample size and inclusion only of hospitalized infants. We could also not get IL 6 levels and CT chest done due to limited resources, although recent published studies have questioned the routine use of CT scans among children with COVID-19. [15, 16].

Our case series shows that infants can develop severe COVID disease, particularly in those who have SAM and anemia, although larger studies are needed to confirm this.

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