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Case report

Clinical features and outcomes of coronavirus disease 2019 in early infants in Japan: A case series and literature review

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ABSTRACT

The clinical picture in early infants with COVID-19 has been described in a limited number of reports, mainly from European countries, United States, and China, but not Japan. Although several reports suggested that early infants can develop more severe COVID-19 disease than older children, risk factors for severe illness and differences according to nationality or ethnicity remain unclear. We report a case series of 13 infants ≤90 days old with COVID-19 in Japan. All patients had mild outcomes and did not require respiratory support or intensive care.

1. Introduction

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly expanded worldwide [1]. The clinical presentation and severity of COVID-19 have been well described in children and adolescents. Previous studies have shown that children generally develop a milder phenotype than adults [2]. By contrast, there are limited reports on the clinical picture in early infants. One systematic review of early infants with COVID-19 reported that admission to the intensive care unit (ICU) and respiratory support were required in approximately 20%–30% of the patients [3]. A few case series showed various degrees of severity of COVID-19 in early infants [4,5]. Risk factors for severe illness remain unclear. In addition, differences in clinical course according to nationality or ethnicity also remain unclear. Previous reports of early infancy have been published mainly from European countries, the United States, and China, but not Japan. In this study, we present a case series of early infants with COVID-19 in Japan and a review of the literature to examine factors contributing to the disease severity.

2. Case report

This study site was the National Center for Child Health and Development, a tertiary care children's hospital accepting patients from all over Tokyo, the capital of Japan. We conducted a retrospective case series study of COVID-19 infants younger than 90 days hospitalized between July 2020 and August 2021. In this institution all COVID-19 positive patients are admitted during this period as per the Infectious Disease Control Law. This disease was confirmed by positivity in a reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 in nasopharyngeal swabs. We collected demographic and clinical characteristics, medical history, laboratory data, and radiological findings from the electronic medical records. We classified the patients according to the severity based on the guidelines from the World Health Organization [6]. Categorical variables were expressed as numbers of cases and percentage, and continuous variables were expressed as the mean/median with IQR/range. Informed consent was obtained from all the patient's parents with opt-out possibility. This study was approved by the Ethics Committees of the National Center for Child Health and Development in September 2021 (#2021–129).

Between July 2020 and August 2021, 226 children with COVID-19 were hospitalized in our hospital. Among these patients, we identified 13 infants (5.8%) younger than 90 days. Clinical characteristics, laboratory data, and imaging findings are summarized in Table 1. The mean age at presentation was 52 days (range 16–86 days). Male infants represented 38% of the patients. Most of the patients were Japanese. All 13 patients had household contact with confirmed COVID-19 patients, and about half of them received diagnoses of COVID-19 during contact tracing. There was no history suggestive of vertical infection, such as episodes of maternal infection or onset of disease in patients less than 14

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Table 1
Clinical characteristics, laboratory data, and imaging findings of early infants with COVID-19.

Characteristics	Total (n = 13)
Age at presentation, days, mean (range)	52 (16–86)
Male, n (%)	5 (38)
Japanese, n (%)	12 (92)
Contact with individual confirmed COVID-19, n (%)	13 (100)
Identified during contact tracing, n (%)	6 (46)
Comorbid conditions, n (%)	3 (23)
Hospital admission, n (%)	13 (100)
ICU admission, n (%)	0
Respiratory support, n (%)	0
Intravenous antibiotics, n (%)	2 (15)
Antiviral drug, n (%)	0
Corticosteroid therapy, n (%)	0
Multisystem inflammatory syndrome in children, n (%)	0
Death, n (%)	0
Clinical symptoms	
Fever, n (%)	8 (62)
Maximum temperature, °C, mean (range)	38.1 (37.2–39.6)
Duration of fever, days, median (range)	1 (0–2)
Rhinorrhea, n (%)	9 (69)
Cough, n (%)	7 (54)
Respiratory distress, n (%)	0
Apnea, n (%)	0
Hypoxia, n (%)	0
Vomiting, n (%)	2 (15)
Diarrhea, n (%)	0
Poor feeding, n (%)	7 (54)
Seizure, n (%)	0
Cold extremities, n (%)	4 (31)
Conjunctivitis, n (%)	0
Asymptomatic, n (%)	1 (8)
Laboratory and imaging studies (n = 9)	
White blood cell count ($\times 10^9$/L), median (range)	7.67 (4.98–12.3)
Absolute neutrophil count ($\times 10^9$/L), median (range)	1.69 (0.47–3.14)
Absolute lymphocyte count ($\times 10^9$/L), median (range)	5.57 (2.64–9.41)
Platelet count ($\times 10^9$/L), median (range)	38 (17–60)
CRP (mg/dL), median (range)	0.02 (0.01–0.42)
AST (U/L), median (range)	34 (22–79)
ALT (U/L), median (range)	19 (11–45)
LDH (U/L), median (range)	279 (183–416)
CK (U/L), median (range)	110 (59–174)
Blood culture, n positive/n obtained	0/7
Urine culture, n positive/n obtained	0/5
Other virus[a] detection by multiplex PCR, n positive/n obtained (%)	1/3 (33)
Chest radiograph abnormal, n/n obtained (%)	4/7 (57)
Computed tomography, n (%)	0

Abbreviations: ICU, intensive care unit; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; PCR, polymerase chain reaction.
[a] Human rhinovirus/enterovirus co-infection.

days old. Three (23%) patients had comorbidities as follows: a preterm infant at 34 weeks of gestation (n = 1), small ventricular septal defect (1 mm in diameter) (n = 1), and feeding disorder requiring nasogastric tube feeding (n = 1). The frequent symptoms were rhinorrhea (69%), fever (62%), cough (54%), poor feeding (54%), and cold extremities (31%). The median duration of fever (≥38.0 °C) and maximum temperature was 1 day (range: 0–2 days) and 38.1 °C (range: 37.2 °C–39.6 °C), respectively. Two (15%) presented with vomiting, but no one had diarrhea. No patients had respiratory distress, apnea, hypoxia, seizure, or conjunctivitis. One patient had no symptoms during the disease course. Blood examinations on admission were performed in 9 of 13 patients, with a median duration of 2 days after onset (range: 1–5 days). Median value of C-reactive protein was 0.02 mg/dL (range: 0.01–0.42 mg/dL). Aspartate aminotransferase, alanine aminotransferase, creatine kinase, and lactate dehydrogenase levels were normal, except for one preterm patient with a mildly elevated aspartate aminotransferase of 79 U/L and lactate dehydrogenase of 416 U/L. The patient had rhinorrhea, cough, and poor oral feeding, but no fever. No patients presented with leukocytosis, lymphocytosis, or lymphocytopenia. Two patients showed neutropenia (0.47×10^9/L and 0.74×10^9/L). Blood and urine cultures were performed in 7/13 (54%) and 5/13 (38%) patients, respectively, with negative results in all the patients. Among them, empirical antibiotics were administered in two patients. The remaining 6 patients without blood cultures did not receive any antibiotics. Finally, no patients had bacterial coinfections detected. Among 7 patients who underwent chest X-ray, 4 (54%) had pulmonary infiltrates. No patients underwent computed tomography. No patients received respiratory support or antiviral drugs (such as remdesivir) or required ICU admission. None of the patients had multisystem inflammatory syndrome in children (MIS-C) as a diagnosis. In all 13 patients, the severities of COVID-19 were mild, and the clinical course was uneventful.

We summarized case series and reviews reporting early infants with COVID-19 (Table 2). Most patients were mildly ill, but one systematic review included many patients that required ICU admission and respiratory support. Severe cases were characterized by co-infection (urinary tract infection or respiratory syncytial virus infection), congenital heart disease, immunodeficiency, preterm birth, or MIS-C.

3. Discussion

This study reports clinical characteristics of COVID-19 in infants less than 90 days old in Japan. All 13 patients had mild outcomes and did not require respiratory support or intensive care. Thus far, only a few case series of early infants with COVID-19 have been available, and risk factors for severity remain unclear. A case series from Saudi Arabia suggested that infants ≤90 days old can develop more severe COVID-19 disease than older children [4].

Early infants with severe COVID-19 described in this review included those with severe pre-existing medical conditions (cyanotic heart disease, immunodeficiency, or extreme prematurity), MIS-C, or co-infection [3,4,7]. Our cases did not involve severe comorbidities or MIS-C. There was one patient with premature birth and one patient with congenital heart disease, both of whom had a mild course of COVID-19. This outcome may be because the degree was mild in the 34-week birth and small ventricular septal defect cases, respectively. So far, the four rhinovirus/enterovirus co-infection patients reported, including ours, all had favorable outcomes. It is still unclear whether co-infection with any virus is more likely to cause severe disease because of the small number of cases in which multiplex PCR was performed in both our study and previous studies. These data suggest that a major risk factor for early infants can be a severe pre-existing medical condition, such as cyanotic heart disease or immunodeficiency.

Other case series with similar conditions to our study also showed a mild clinical course of COVID-19 except for one case with bacterial co-infection [5,7]. In contrast, the systematic reviews have shown that early infants with COVID-19 require more intensive care and respiratory support than older children [3,11,12,]. This difference in severity may be due to the younger age of the patients in the review and the inclusion of more case reports that are prone to publication bias. As the case series summarized here does not include early neonates or cases of vertical infection, it may be necessary to consider early neonates as a separate group among early infants younger than 90 days.

Our results showed that respiratory symptoms were more prevalent than gastrointestinal symptoms. This finding is consistent with previous case series, including asymptomatic patients [5]. Although one case series reported patients ≤90 days had a predominance of gastrointestinal syndromes (13/14, 93% of patients), this study included only symptomatic cases, and might have had selection bias [10].

Table 2
Summary of early infants with COVID-19.

	This study	Mithal et al. [5]	Shaiba et al. [4]		Blázquez-Gamero et al. [7]	McLaren et al. [8]	Hassoun et al. [9]	Panetta et al. [10]	Trevisanuto et al. [11]	Dhir et al. [12]	Mark et al. [3]
Article type	Case series	Case series	Case series		Case series	Case series	Case series	Case series	Systematic review	Systematic review	Systematic review
	Younger than 90 days	Younger than 90 days	Younger than 90 days		Younger than 90 days Fever without source	Younger than 60 days	Younger than 60 days Patients with fever	Younger than 1 year (Except for less than 3 months)	Younger than 30 days	Younger than 30 days	Younger than 90 days
Total (N)	13	18	16 (Neonatal)	20 (Post-neonatal)	27	7	8	14	44	58	63
Age at presentation, days, median (IQR)	50 (27–72)	56 (40–75)	17.5 (1–27) (range)	61 (29–90) (range)	26 (16–40)	39 (16–49)	42 (22–48)	34 (23–65)	10 (2–19)	3 (1–12), (n = 44)	5 days to < 3 months
Male, n/N (%)	5/13 (38)	7/18 (39%)	11/16 (69)	9/20 (45)	17/27 (63)	6/7 (86)	6/8 (75)	7/14 (50)	18/31 (58)	NA	42/61 (69)
Nation, n/N (%)	Japanese 12/13 (92)	Latinx 14/18 (78)	Saudi Arabia 36/36 (100)		Spain 27/27 (100)	USA 7/7 (100)	African American 4/8 (50) White 2/8 (25) Hispanic 1/8 (13) South Asian Indian 1/8 (13)	Canada 14/14 (100)	China 16/44 (36) Italy 8/44 (18) UK 6/44 (14) France 5/44 (11) Others 9/44 (20)	UK 12/39 (31) Spain 8/39 (21) Italy 7/39 (18) China 5/39 (13) USA 3/39 (8) Others 4/39 (10)	USA 22/63 (35) China 11/63 (17) France 11/63 (17) Italy 9/63 (14) UK 4/63 (6) Others 6/63 (10)
Comorbid conditions, n/N (%)	3/13 (23) Prematurity (34 weeks) (n = 1) Small VSD (n = 1) Feeding disorder (n = 1)	0/18	3~/20 Prematurity (n = 1) Large VSD (n = 1) TGA, VSD, ASD (n = 1)	0/20 NA	5/27 (18.5) Prematurity (35 and 36 weeks) (n = 2) Shwachman-Diamond syndrome (n = 1) Congenital heart disease (n = 1) Phenylketonuria (n = 1)	2/7 (29) Congenital heart disease (n = 1) Multiple abnormalities (n = 1)	1/8 (13) Dysplastic kidney and imperforate anus (n = 1)	1/14 (7) Prematurity (n = 1)	NA NA	NA	7/41 (17)[d] Congenital heart disease (n = 3) Cystic fibrosis (n = 1) Renal anomalies (n = 3)
Hospital admission, n/N (%)	13/13 (100)	9/18 (50)	14/16 (88)	9/20 (45)	24/27 (89)	7/7 (100)	8/8 (100)	8 (57)	44/44 (100)	NA	58 (92)
ICU admission, n/N (%)	0/13	0/18	2/16 (13)	2/20 (10)	1/27 (4)	0/7	0/8	1/14 (7)	NA	23/38 (61)	13/61 (21)
Respiratory support, n/N (%)	0/13	0/18	2/16 (13)	2/20 (10)	0/27	0/7	0/8	0/14	6/36 (17)	11/37 (30)	14/58 (24)
Death, n/N (%)	0/13	0/18	0/16	1/20 (5)	0/27	0/7	0/8	0/14	0/44	NA	0/63
Severe	0/13	0/18	Large VSD (n = 1) TGA, VSD, ASD (n = 1)	MIS-C (n = 2)	Urinary tract infection by *Escherichia coli* (n = 1)	0/7	0/8	Urosepsis from *Escherichia coli* (n = 1)	NA	NA	Extreme prematurity Myocarditis Sepsis RSV coinfection
Clinical symptoms											
Fever, n/N (%)	8/13 (62)	14/18 (78)	9/16 (56)	16/20 (80)	27 (100)[c]	7/7 (100)	7/8 (88)	10/14 (71)	17/34 (50)	NA	46 (73)
Respiratory symptoms[a], n/N (%)	11/13 (85)	10/18 (56)	11/16 (69)	11/20 (55)	0/27	2/7 (29)	4/8 (50)	6/14 (43)	7/34 (20)	NA	40 (66)

(*continued on next page*)

Table 2 (*continued*)

	This study	Mithal et al. [5]	Shaiba et al. [4]		Blázquez-Gamero et al. [7]	McLaren et al. [8]	Hassoun et al. [9]	Panetta et al. [10]	Trevisanuto et al. [11]	Dhir et al. [12]	Mark et al. [3]
Gastrointestinal symptoms[b], n/N (%)	2/13 (15)	4/18 (22)	6/16 (38)	5/20 (25)	0/27	1/7 (14)	2/8 (25)	13/14 (93)	9/34 (26)	NA	Vomiting 9 (14) Diarrhea 9 (14)
Hypoxia, n/N (%)	0/13	0/18	1/16 (6)	1/20 (5)	0/27	0/7	0/8	0/14	7/35 (20)	NA	9 (14)
Asymptomatic, n/N (%)	1/13 (8)	1/18 (6)	1/16 (6)	1/20 (5)	0/27	0/7	0/8	NA	12/38 (32)	16/43 (37%)	3 (5)
Laboratory and imaging studies											
White blood cell count ($\times 10^9$/L), median (IQR)	7.67 (6.77–9.52), (n = 9)	8.30 (6.23–9.88), (n = 12)	Mean (range) 8.24 (2.8–17.9) non-severe (n = 32) 10.15 (8.25–15.8), severe (n = 4)		6.10 (4.29–8.07), (n = 27)	7.00 (5.45–8.45), (n = 7)	7.05 (6.58–10.8), (n = 8)	10.5 (7.60–14.1)	NA	NA	7.04 (4.80–8.94), (n = 44)
Absolute neutrophil count ($\times 10^9$/L), median (IQR)	1.69 (1.22–1.70), (n = 9)	2.64 (1.62–4.58), (n = 12)	3.98 (2.18–7.17), severe (n = 4)		1.30 (0.905–2.36), (n = 27)	2.66 (1.41–3.44), (n = 7)	2.42 (1.08–3.64), (n = 8)	3.10 (2.10–8.30)	NA	NA	1.20 (0.87–1.99), (n = 36)
CRP (mg/dL), median (IQR)	0.02 (0.02–0.04), (n = 9)	0.1, <0.1, (n = 2)	7.0 (2.8–22.3), severe (n = 4)		1.9 (0.6–5), (n = 27)	1.2 (0.85–3.1), (n = 7)	≤0.38, (n = 6)	>10, (n = 3)	NA	NA	2.1 (0.9–4.5), (n = 27)
Chest radiograph abnormal, n/N obtained (%)	4/7 (57)	0/5	13/23 (57)		3/6 (50)	0/4	1/4 (25)	2/7 (29)	15/21 (71)	NA	13/28 46)
Other virus detection by multiplex PCR, n positive/N obtained (%)	1/3 (33) Rhinovirus/ Enterovirus	0/5	NA	NA	0/6	NA	1/3 (33) Rhinovirus/ Enterovirus	NA	NA	NA	5/30 (17) RSV (n = 2) Rhinovirus/ Enterovirus (n = 2) Seasonal coronavirus (n = 1)
Blood culture, n positive/N obtained (%)	0/7	0/12	0/15	0/16	1/24 (4) *Streptococcus mitis* (n = 1)	0/7	0/8	NA	2/13 (15)	NA	1/37 (3) *Streptococcus epidermidis* (n = 1)
Urine culture, n positive/N obtained (%)	0/5	1/12 (8) *Streptococcus agalactiae* *Klebsiella oxytoca*	2/15 (13) *Klebsiella pneumoniae* (n = 1) NA (n = 1)	0/16	2/26 (8) *Escherichia coli* (n = 1) *Enterobacter cloacae* (n = 1)	2/7 (29) *Escherichia coli* (n = 2)	1/5 (20) *Escherichia coli*	4/14 (29) *Escherichia coli* (n = 4)	NA	NA	3/28 (11) *Escherichia coli* (n = 2) *Klebsiella oxytoca* (n = 1)

Abbreviations: ICU, intensive care unit; CRP, C-reactive protein; VSD, ventricular septal defect; ASD, atrial septal defect; TGA, transposition of great arteries; PCR, polymerase chain reaction; NA, not applicable; MIS-C, multisystem inflammatory syndrome in children; RSV, respiratory syncytial virus.
References are denoted by parentheses.

[a] Defined as cough, congestion, rhinorrhea, respiratory distress, or apnea.

[b] Defined as diarrhea or vomiting.

[c] Case series of infants with SARS-CoV-2 infection and fever without source.

[d] Except for preterm.

The main laboratory findings in our study, including mild elevation of aminotransferase values and neutropenia, are consistent with previous reports [3,7]. We also found that more than half of the patients who had chest X-rays had pulmonary infiltrates despite their mild clinical course. This result suggested that a chest X-ray might not help determine the severity of COVID-19 in early infants.

Differences in children with COVID-19 according to nationality or ethnicity have not been adequately examined, with only a case series of an over-representation of Latinx ethnicity [5]. A systematic review of mostly Chinese children found that neonates and children under one year were more vulnerable to more severe COVID-19 disease than older children [13]. By contrast, there were no severe cases in our Japanese patients. Further studies are needed to determine whether Asians are more susceptible to severe disease. This study is limited by the small number of cases from a single center and the retrospective observational study design. Due to the bias in the patients' nationality, this case series might not be generalizable to other populations. However, to our knowledge, this is the first Japanese case series, which contributes to the accumulation of data on diverse populations.

In conclusion, we described 13 patients less than 90 days old with COVID-19. Half of them were identified during contact tracing. All had a mild clinical course and respiratory symptoms predominated over gastrointestinal symptoms.

Authorship statement

HI wrote the first draft of the manuscript. TF and MK modified and reviewed the manuscript. MK supervised and revised the manuscript. All authors approved the final manuscript.

Declaration of competing interest

All authors do not have any potential, perceived, or real conflicts of interest.

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