European Journal of Pediatrics (2021) 180:3041–3045
https://doi.org/10.1007/s00431-021-04042-x

SHORT COMMUNICATION

Clinical characteristics of COVID-19 in neonates and young infants

Vana Spoulou[1] · Maria Noni[1] · Dimitra Koukou[1] · Athanasios Kossyvakis[2] · Athanasios Michos[1]

Received: 6 November 2020 / Revised: 18 March 2021 / Accepted: 21 March 2021 / Published online: 31 March 2021

Abstract

We report the clinical characteristics and management of fourteen neonates and very young infants with COVID-19. Although all presented with mild symptoms and did not require specific treatment, most of them had abnormal laboratory and radiological findings. Ten infants presented with neutropenia and/or monocytosis but none with lymphopenia. Transient hypertriglyceridemia and/or prolonged viral shedding were detected in 9 patients.

Conclusion: Based to our experience, COVID-19 is mild in very young infants and might have distinct laboratory findings.

What is Known:
• *SARS-CoV-2 in infants is a mild disease.*
• *The period of transmission is approximately 2 weeks.*
What is New:
• *Very young age is not a risk factor for severe COVID-19 but could be associated with prolonged viral shedding.*
• *Neutropenia and monocytosis are distinct characteristics of COVID-19 in very young infants.*

Keywords COVID-19 · Infants · SARS-CoV-2 · Pandemic

Abbreviations

BPD	Bronchopulmonary dysplasia
RT-PCR	Real-time reverse transcriptase polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Communicated by Nicole Ritz

✉ Vana Spoulou
vspoulou@med.uoa.gr

Maria Noni
marianoni21@gmail.com

Dimitra Koukou
dmkoukou@gmail.com

Athanasios Kossyvakis
akossivakis@pasteur.gr

Athanasios Michos
amichos@med.uoa.gr

[1] 1st Department of Pediatrics, "Aghia Sophia" Children's Hospital, National and Kapodistrian University of Athens, Athens, Greece

[2] National Reference Laboratory for Influenza and other Respiratory Viruses, Hellenic Pasteur Institute, Athens, Greece

Introduction

Since December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first appeared in China, has spread rapidly across the world affecting all ages. Even though the fact that the heaviest death toll has been paid by the elderly, pediatric populations have also been affected. However, the number of affected children worldwide is relatively small. A review of 72,314 cases by the Chinese Center for Disease Control and Prevention showed that children younger than 10 years of age represented less than 1% of all cases [1]. The numbers are even smaller for neonates and infants as shown in a report from the USA where children <1 year represented the 0.27% of patients of all ages [2]. Moreover, the clinical presentation of pediatric COVID-19, the disease caused by SARS-CoV-2, is significantly different than in the elderly and all reports highlight that the majority of infants and

children present with mild symptoms and very low mortality [3, 4]. However, there is still uncertainty regarding risk factors associated with more severe disease in pediatric populations. Very young age could be a potential risk factor for community-acquired COVID-19, due to the immaturity of immune system in early life, which is associated with increased severity to many viral infections [5].

Since the literature of the disease presentation and outcome in early life is sparse, there is a clear knowledge gap for the clinical management of neonates and very young infants with community acquired SARS-CoV-2. In this report, we present the clinical management of 14 neonates and very young infants under 3 months of age that have been admitted to the COVID-19 Unit of "Aghia Sophia" Children's which is the largest tertiary Children's Hospital in Greece during the first 7 months of the pandemic.

Methods

All neonates and young infants of our study were outpatients who were found positive for SARS-CoV-2 in the emergency department and were admitted to the dedicated COVID-19 Unit of our hospital. Confirmed cases were defined through nasal and/or pharyngeal swabs positive for the presence of SARS-CoV-2 viral RNA using an in-house Taqman rt-real-time PCR assay targeting E and RdRP genes. Assay validation was performed in line with ISO 15189: 2012 requirements. The quality of COVID-19 diagnostic testing was supported and ensured by proficiency testing panels, i.e., external quality assessment (EQA) schemes provided by ECDC and WHO.

Results

Between February and September 2020, 253 neonates and young infants under 3 months of age were tested for SARS-CoV-2 and 14 (5.5%) were found positive with cycle threshold values between 15.1 and 37.4 Eleven infants were male (79%). The youngest was aged 11 days and the oldest 87days (Table 1). Eleven infants (78.5%) had at least one parent tested positive for SARS-CoV-2 and in 9 cases, the source of infection was the mother. One infant had travel history before the onset of infection while both parents tested negative for SARS-CoV-2. The source of infection in the rest two infants was a family member other than the parents. In all cases, the maternal history during delivery was negative for COVID-19 and all infants have been infected after delivery.

Upon admission, 11 (79%) infants had fever up to 39 °C. Other symptoms included rhinorrhea (n=9; 64%), cough (n=3; 21%), diarrhea (n=4; 28.5%), drowsiness (n=3; 21%), feeding difficulties (n=3; 21%), and tachypnea (n=2; 14%). One infant was totally asymptomatic.

Chest X-rays were performed in 13 (92.8%) infants and diffuse interstitial infiltration was detected in 7 of them (54%). One infant had extra right upper lobe consolidation. Chest computed tomography (CT) was not considered necessary due to the lack of severe respiratory distress of all patients.

Complete blood count, urine analyses, blood biochemistry, and infection biomarkers were tested upon admission. Laboratory tests revealed neutropenia (n=7; 50%), monocytosis (n=6), or both (n=3; 21%) but not lymphopenia. Viral testing for influenza-A and B virus and respiratory syncytial virus with rapid test was negative in all cases.

On admission, 6 (42.8%) infants received iv antibiotics which were discontinued when cultures returned negative for bacterial co-infection. Three infants required intravenous fluids. Only patient 2 presented with mild respiratory distress and required 0.5 to 2 L/min oxygen through head box as well as salbutamol and budesonide through a spacer for 72 h. According to his past medical history, he was a preterm neonate, born at 30 weeks of gestation, with mild bronchopulmonary dysplasia (BPD). This was the only infant whose clinical condition worsened on the 7th day of hospitalization and received again oxygen through head box for 48 h. Six patients presented with hypertriglyceridemia. Among them, a male infant 69 days of age developed severe hypertriglyceridemia and excessive lipemic serum 6 days after the onset of symptoms. Feeding was stopped and patient received intravenous fluids for 24 h. Patient was monitored closely and hypertriglyceridemia decreased steadily, with no other adverse events. No infant received any antiviral therapy or specific therapy for SARS-CoV-2. During hospitalization, mothers stayed at the same room with their infants to enhance mother-infant bonding and continued breastfeeding.

All patients were discharged 2 to 12 days after admission in excellent condition but still positive for SARS-CoV-2. In follow-up appointments, all patients with positive PCR for more than 20 days had cycle-threshold (Ct) values higher than 30. Seven infants kept shedding the virus for up to 35 days from the initial diagnosis (Table 1).

Discussion

In the present report, we describe our experience from the largest pediatric tertiary hospital of Greece during the first 7 months of the SARS-CoV-2 epidemic. Among 253 hospitalized neonates and young infants up to 3 months of age, with symptoms compatible with COVID-19, only 14 (5.5%) were detected positive for the virus.

The most common source of infection was an asymptomatic or mildly symptomatic family member suggesting that close contact within the family increases significantly the risk of transmission [6, 7].

Table 1 Epidemiological and clinical characteristics of infants hospitalized with confirmed SARS-CoV-2 infection

Characteristics	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10	Pt 11	Pt 12	Pt 13	Pt 14
Age (days)	11	18	48	58	87	71	28	38	69	77	78	78	45	27
Sex	Male	Male	Male	Male	Male	Male	Male	Female	Male	Male	Female	Male	Male	Female
Source of transmission														
Parents	Yes	Yes	No*	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Signs and symptoms														
Fever (maximum axillary temperature)	37.6 °C	38.1 °C	37.7°C	39.0 °C	37.6 °C	38.7 °C	No	37.8°C	38.0°C	39.0°C	38.3°C	No	No	37.6°C
Cough	No	No	No	Yes	Yes	No	No	No	Yes	No	No	No	No	No
Rhinorrhea	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	Yes	No
Tachypnea	No	No	No	No	Yes	No	No	No	No	Yes	No	No	No	No
Diarrhea	No	No	No	Yes	Yes	Yes	No	No	No	Yes	No	No	No	No
Drowsiness	No	No	Yes	No	No	Yes	No	No	No	Yes	No	No	No	No
Feeding difficulties	No	No	Yes	No	No	No	No	No	No	Yes	No	No	Yes	No
Chest X-ray findings														
Diffuse interstitial infiltration	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	NA	No	No
Lobe consolidation	No	Yes	No	No	No	No	No	No	No	No	No	NA	No	No
Laboratory results (reference values)														
Leukocytes ($\times 10^9$ L^{-1}; normal range 6–17.5)	9.3	6.8	6.9	7.41	4.5	5.8	8.22	11.59	12.62	9.12	6.6	13.03	4.46	12.13
Neutrophils ($\times 10^9$ L^{-1}; normal range 1.5–8.5)	2.0	0.86	1.6	0.96	0.76	0.52	1.9	2.2	2.4	2.0	1.2	2.6	0.38	1.09
Lymphocytes ($\times 10^9$ L^{-1}; normal range 2.0–10.5)	3.7	4.06	4.1	4.2	2.3	4.08	4.5	7.1	8.0	5.2	3.6	7.1	2.67	8.61
Monocytes ($\times 10^9$ L^{-1}; normal range 0.2–1.2)	2.95	0.49	0.83	0.7	1.4	1.05	0.82	1.3	1.0	1.3	1.4	1.1	1.11	1.33
Platelets ($\times 10^9$ L^{-1}; normal range 140–440)	350	328	277	565	302	408	455	332	555	425	401	505	319	283
Hemoglobin (g dL^{-1}; normal range 10.5–14.5)	16.5	10.8	9.2	8.7	11.8	10.2	10.5	8.1	9.1	9.6	10.1	9.8	12	14.3
CRP (mg L^{-1}; normal range 1.0–10.0)	1.38	12.1	1.97	4.89	1.89	1.2	2.2	1.2	1.0	3.5	4.6	2.1	1.84	2.2
ALT (U L^{-1}; normal range 5–45)	18	22	17	57	43	49	22	75	43	86	31	42	33	47
AST (U L^{-1}; normal range 10–60)	41	45	30	78	69	26	13	26	20	26	18	15	11	38
BUN (mg dL^{-1}; normal range 10–35)	10	5	10	15	20	17	14	18	14	15	24	8	17	22
Cr (mg dL^{-1}; normal range 0.2–1.0)	0.28	0.3	0.19	0.28	0.24	0.23	0.24	0.28	0.23	0.16	0.2	0.23	0.3	0.23
CK (U L^{-1}; normal range <140)	156	NA	316	117	NA	222	NA	NA	144	205	NA	88	26	81
LDH (U L^{-1};s normal range 120–300)	349	494	273	341	635	403	295	688	718	967	NA	390	350	412
Triglycerides (mg dL^{-1}; normal range 30–130)	98	86	85	100	105	220	140	82	2959	150	121	230	156	73
Duration of hospitalization (days)	4	12	2	7	12	5	4	4	5	4	3	4	2	3
Days of positive SARS-CoV-2 RT-PCR since admission	NA	26	28	35	NA	22	11	NA	25	NA	NA	12	NA	NA

*Travel abroad

Pt, patient; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *BUN*, blood urea nitrogen; *S Cr*, serum creatinine; *CK*, creatine kinase; *LDH*, lactate dehydrogenase; *CRP*, C-reactive protein; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *NA*, not available

All infants presented with mild symptoms but were hospitalized due to their very young age. Interestingly, even the infant with BPD which is a risk factor for severe respiratory disease caused by other respiratory viruses, e.g., RSV and influenza did not develop severe respiratory symptoms. This is in accordance with previous reports where the majority of neonates and infants with COVID-19 had atypical or mild clinical presentation [8].

Neutropenia and/or monocytosis was detected in 10 infants (71.4%) while none of them experienced lymphopenia which has consistently been reported in adults and has been associated with increased disease severity [9]. The lack of lymphopenia, possibly attributed to the high thymic output in early life, in association with the relative immaturity of monocytes which results in diminished cytokine responses, could be a smart way of the neonatal immune system to response to SARS-CoV-2 without excessive inflammation associated with severe lung disease [10].

It appears that there is a pattern of dyslipidemia that may be characteristic of patients with COVID-19. Also, severe triglyceride abnormalities attributed to SARS-CoV-2-induced inflammation have been associated with pancreatitis in adults [11]. This was not the case in our patient who developed severe hypertriglyceridemia but with no other sequelae. Both his parents were tested negative for familiar hypertriglyceridemia.

Accumulating evidence with regard to treatment of COVID-19 in early life indicates that very few neonates require additional treatment, with antiviral agents, azithromycin, or a-interferon which reflects the current uncertainties regarding specific treatment options [3, 9, 12]. All our patients were, rapidly improved without any specific treatment, providing further evidence that additional treatment is not necessary for a favor outcome of community-acquired COVID-19 in neonates and very young infants. However, the substantial number of infants who received iv antibiotics until the exclusion of bacterial co-infection justifies the increasing concern of a possible negative impact of the virus on antibiotic stewardship.

Interestingly, in contrast to what has been reported for older children with COVID-19 [13], 5 infants had positive PCR for more than 3 weeks although with high Ct values which was suggestive that the virus was not transmissible [14].

The radiological findings in most infants were non-specific and similarly to what has been previously reported in pediatric populations, there was no need for routinely performing chest CT [15]. Since SARS-CoV-2 continues to spread, it is important to identify risk factors for severe COVID-19 among pediatric populations. According to our experience, COVID-19 in very young age presents with distinct laboratory findings and has a favorable outcome without specific treatments.

Availability of data and material All data are available.

Authors' contributions Vana Spoulou and Athanasios Michos contributed to the study conception and design. Material preparation and data collection were performed by Maria Noni and Dimitra Koukou. All authors read and approved the final manuscript.

Declarations

Ethic statement and consent statement Consent was not required as long as complete anonymity was achieved and the submission did not include data that may identify patients.

Conflict of interest The authors declare no competing interests.

References

1. Wu Z, McGoogan JM (2020) Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 323:1239
2. Coronavirus disease 2019 in children - United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(14):422-6.
3. Götzinger F, Santiago-García B, Noguera-Julián A, Lanaspa M, Lancella L, Calò Carducci FI, Gabrovska N, Velizarova S, Prunk P, Osterman V, Krivec U, Lo Vecchio A, Shingadia D, Soriano-Arandes A, Melendo S, Lanari M, Pierantoni L, Wagner N, L'Huillier AG, Heininger U, Ritz N, Bandi S, Krajcar N, Roglić S, Santos M, Christiaens C, Creuven M, Buonsenso D, Welch SB, Bogyi M, Brinkmann F, Tebruegge M, Pfefferle J, Zacharasiewicz A, Berger A, Berger R, Strenger V, Kohlfürst DS, Zschocke A, Bernar B, Simma B, Haberlandt E, Thir C, Biebl A, vanden Driessche K, Boiy T, van Brusselen D, Bael A, Debulpaep S, Schelstraete P, Pavic I, Nygaard U, Glenthoej JP, Heilmann Jensen L, Lind I, Tistsenko M, Uustalu Ü, Buchtala L, Thee S, Kobbe R, Rau C, Schwerk N, Barker M, Tsolia M, Eleftheriou I, Gavin P, Kozdoba O, Zsigmond B, Valentini P, Ivaškeviciene I, Ivaškevicius R, Vilc V, Schölvinck E, Rojahn A, Smyrnaios A, Klingenberg C, Carvalho I, Ribeiro A, Starshinova A, Solovic I, Falcón L, Neth O, Minguell L, Bustillo M, Gutiérrez-Sánchez AM, Guarch Ibáñez B, Ripoll F, Soto B, Kötz K, Zimmermann P, Schmid H, Zucol F, Niederer A, Buettcher M, Cetin BS, Bilogortseva O, Chechenyeva V, Demirjian A, Shackley F, McFetridge L, Speirs L, Doherty C, Jones L, McMaster P, Murray C, Child F, Beuvink Y, Makwana N, Whittaker E, Williams A, Fidler K, Bernatoniene J, Song R, Oliver Z, Riordan A (2020) COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adoles Health 4(9):653–661
4. Viner RM, Mytton OT, Bonell C, Melendez-Torres GJ, Ward J, Hudson L et al (2020) Susceptibility to SARS-CoV-2 infection among children and adolescents compared with adults: a systematic review and meta-analysis. JAMA Pediatr
5. Simon AK, Hollander GA, McMichael A (2015) Evolution of the immune system in humans from infancy to old age. Proc Biol Sci 282(1821):20143085
6. Raschetti R, Vivanti AJ, Vauloup-Fellous C, Loi B, Benachi A, De Luca D (2020) Synthesis and systematic review of reported neonatal SARS-CoV-2 infections. Nat Commun 11(1):5164
7. Antúnez-Montes OY, Escamilla MI, Figueroa-Uribe AF, Arteaga-Menchaca E, Lavariega-Saráchaga M, Salcedo-Lozada P, Melchior P, de Oliveira RB, Tirado Caballero JC, Redondo HP, Montes Fontalvo LV, Hernandez R, Chavez C, Campos F, Uribe F, del Aguila O, Rios Aida JA, Buitrago AP, Betancur Londoño LM, Mendoza Vega LF, Hernández CA, Sali M, Higuita Palacio JE, Gomez-Vargas J, Yock-Corrales A, Buonsenso D (2021)

COVID-19 and multisystem inflammatory syndrome in Latin American children: a multinational study. Pediatr Infect Dis J 40(1):e1–e6
8. De Bernardo G, Giordano M, Zollo G, Chiatto F, Sordino D, De Santis R et al (2020) The clinical course of SARS-CoV-2 positive neonates. J Perinatol 40(10):1462–1469
9. Kanburoglu MK, Tayman C, Oncel MY, Akin IM, Can E, Demir N, Arayici S, Baser DO, Caner I, Memisoglu A, Uygun SS, Akar S, Akin MA, Ataoglu E, Bezirganoglu H, Bilgin L, Bozdag S, Comert S, Gurpinar R, Imamoglu EY, Imdadoglu T, Narter F, Ozdemir R, Toptan HH, Yalinbas EE, Yaman A, Erdeve O, Koc E (2020) A multicentered study on epidemiologic and clinical characteristics of 37 neonates with community-acquired COVID-19. Pediatr Infect Dis J 39(10):e297–e302
10. Kollmann TR, Levy O, Montgomery RR, Goriely S (2012) Innate immune function by Toll-like receptors: distinct responses in newborns and the elderly. Immunity. 37(5):771–783
11. Wei X, Zeng W, Su J, Wan H, Yu X, Cao X, Tan W, Wang H (2020) Hypolipidemia is associated with the severity of COVID-19. J Clin Lipidol 14(3):297–304
12. Piersigilli F, Carkeek K, Hocq C, van Grambezen B, Hubinont C, Chatzis O, van der Linden D, Danhaive O (2020) COVID-19 in a 26-week preterm neonate. Lancet Child Adoles Health 4(6):476–478
13. Bahar B, Jacquot C, Mo YD, DeBiasi RL, Campos J, Delaney M (2020) Kinetics of viral clearance and antibody production across age groups in children with severe acute respiratory syndrome coronavirus 2 infection. J Pediatr S0022-3476(20):31114–31118
14. Liotti FM, Menchinelli G, Marchetti S, Posteraro B, Landi F, Sanguinetti M, Cattani P (2020) Assessment of SARS-CoV-2 RNA test results among patients who recovered from COVID-19 with prior negative results. JAMA Intern Med
15. Buonsenso D, Parri N, De Rose C, Valentini P (2021) Toward a clinically based classification of disease severity for paediatric COVID-19. Lancet Infect Dis 21(1):22