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Case Report

Case report of a neonate with high viral SARSCoV-2 loads and long-term virus shedding

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ABSTRACT

Background: SARS-CoV-2 has spread globally. Currently, literature of SARS-CoV-2 in neonates is scarce. We present a case of a neonate with a high viral load and prolonged virus shedding.
Methods: Epidemiology, clinical characteristics, treatment, laboratory data and follow-up information and the treatment of a neonate with COVID-19 were recorded.
Results: A 7-day-old boy was admitted to the hospital with fever, lethargy and apnoea. He was found SARS-CoV-2 RNA positive with an exceptionally high viral load in nasopharyngeal swab and stool. The father and two maternity nurses at home had detectable SARS-CoV-2 RNA as well. Sequencing showed all strains belonged to the same cluster. The father was asymptomatic and the maternity nurses developed symptoms after visiting. In the mother, no SARS-CoV-2 RNA could be found. Six days after admission, the neonate was discharged after clinical improvement with oral antibiotics because of a possible pyelonephritis. Monitoring the course of this infection showed that SARS-CoV-2 RNA was detectable in the nasopharynx until day 19 and in stool until day 42 after symptom onset.
Conclusions: This case shows that neonates can have a high viral load of SARS-CoV-2 and can shed the virus for over one month in stool. Despite the high viral load in the neonate, the mother and a sibling did not get infected.

Background

Starting from December 2019, a novel coronavirus (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), has spread on a global scale [1]. Compared to adults, children seem to be less affected by SARS-CoV-2 infection as they are usually asymptomatic or have mild symptoms [1–4]. However, little is known about disease severity in neonates, the need for treatment and their role in transmission of SARS-CoV-2 [5]. It is reported that children or neonates can have high viral loads, while remaining asymptomatic or having mild symptoms [6,7]. However, there is no clear association between the viral load and infectivity.

Furthermore, in children aged between 2 months and 15 years, SARS-CoV-2 RNA could still be detected in their stool in up to 70 days [4,8,9]. Data about duration of viral shedding in neonates is scarce [10,24,27,33].

In this case report we present a 7-day-old neonate who was hospitalized in the Netherlands with COVID-19 and had a high viral load of SARS-CoV-2 in the nasopharynx and stool. We reviewed the literature and investigated the duration of viral shedding and the source of infection. Only detection of viral RNA was described in this article, not the isolation of live virus.

Case presentation

A 7-day old boy was admitted to the emergency ward of the Amphia hospital in Breda, the Netherlands because of fever (rectal temperature 38.4–39.4 °C), lethargy and apnoea. The day before this presentation, he was treated with phototherapy for 1 day for hyperbilirubinemia. He had no runny nose and no tachypnoea, oxygen saturation was 99% on room air, and auscultation of his lungs was clear. All laboratory characteristics are presented in Table 1.

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Table 1
Laboratory characteristics.

Days since positive PCR SARS-CoV-2 neonate	Day-1	Day 0-morning	Day 0-evening	Day 1	Day 2	Day 5
Haemoglobin, g/L	11.8		10.6	11.1	10.3	
White blood cell count, × 10^9/L	7.3		8.6	15.1	7.4	
Lymphocyte count, × 10^9/L			**1.47**		3.84	
Platelet count, × 10^9/L	258		269	254	158	
C-response protein, mg/L	1	1	5	**54**	23	
Alanine aminotransferase, U/L				14		
Aspartate aminotransferase, U/L				51		
Total bilirubin, mmol/L	**362**	229	203	201		
Creatine kinase, U/L				101		
Lactate dehydrogenase, U/L				634	499	
Urine - White blood cell count, × 10^9/L			**>800**			22
Urine - erythrocyt count, × 10^9/L			<5			<5
Lumbar puncture - white blood cell count, × 10^9/L			1			
Lumbar puncture - erythrocyt count, × 10^9/L			1000			
Blood culture			Neg			
Urine culture			Neg			
PCR Enterovirus/ parechovirus (stool)			Neg			
PCR Enterovirus (lumbar fluid)			Neg			
PCR influenza/RSV (nasopharyngeal swab)			Neg			

(Abbreviations: COVID-19 = new coronavirus 2019, PCR = polymerase chain reaction, RSV = respiratoir syncytieel virus, pos = positive, and neg = negative).

Only the first lymphocyte count was low and there was an increase of c-response protein on day 1. Since there were no respiratory symptoms, no chest radiograph was performed. Because of his age, a total sepsis work-up was performed including complete blood count, urinalysis, cerebrospinal fluid (CSF) studies, blood, urine and CSF culture, and nasopharyngeal swab and stool for PCR viruses. After the work-up, empirical therapy for late-onset sepsis (intravenous therapy of amoxicillin and cefotaxime) was initiated. SARS-CoV-2 RNA was detected in a nasopharyngeal swab and stool by a semi-quantitative real-time reverse transcriptase polymerase chain reaction (sqRT-PCR) with low cycle threshold (Ct)-values of 13.9 and 20.5 respectively, suggesting a high viral load [11,12]. No SARS-CoV-2 RNA was found in urine and CSF. sqRT-PCR was negative for other pathogens on nasopharyngeal swab, CSF and stool (Table 1). Blood and urine bacterial culture remained negative. The urine culture could be false negative because of the antibiotics which were administrated prior to the urine sample. Because of that fact and leukocyturia, a possible bacterial pyelonephritis could not be excluded. From three days post-symptom onset, there were no clinical symptoms with stable parameters. Six days after admission, the neonate was discharged in good condition with oral antibiotics (amoxicillin 80 mg/kg) for three more days.

Course of infection

No COVID-19-related symptoms were recorded during the 14 days follow-up after discharge. Nasopharyngeal swab remained SARS-CoV-2 RNA positive until day 19 and became negative after day 20 of disease onset. Stool samples remained positive until day 42 (Fig. 1).

Source of infection

The neonate had been delivered vaginally at term after an uneventful pregnancy and was breastfed. We investigated the source of this infection and Fig. 1 illustrates the dates of exposure, illness onset and sampling and real-time RT–PCR results of nasopharyngeal and rectal swabs of close-contacts of the boy. His parents did not report fever or upper airway complaints. His two-year-old sister had a runny nose for weeks and his grandparents reported a fever with upper airway complaints (runny nose and cough) 28 days before unset of illness of the boy. Maternity nurse 1 (MN1) to.ok care for the neonate for one day at home without symptoms of COVID-19. This happened two days before the neonate had fever for the first time. One day after the visit, she developed a sore throat. Maternity nurse 2 (MN2) started working without symptoms the day after the visit of MN1. She had symptoms of fever, headache and chest pain one day after visit as well. The father, MN1, and MN2 tested SARS-CoV-2 RNA positive, with initial nasopharyngeal Ctvalues 33.3, 18.3 and 26.2 respectively (Fig. 1). Follow-up showed that the father had an increasing viral load on day 6 (Ct-value 21.9). Both mother and sister remained SARS-CoV-2

RNA negative at day 13 and day 19, respectively. Expressed breast milk was tested negative.

Whole genome sequencing of the virus from the nasopharyngeal swab specimens was performed as described before [13]. MN2 and the neonate had identical genomes while the father and MN1 had a difference of 1 single-nucleotide polymorphism, placing all viral genomes in one cluster. A phylogenetic tree was constructed containing all Dutch SARS-CoV-2 sequences using IQ-TREE under the GTR+F+I+G4 as best predicted model using the ultrafast bootstrap option [14,15].

To investigate whether mother and sister had previously been infected and already turned negative SARS-CoV-2 PCR results, serum samples were tested at day 3 and day 19 (mother) and day 19 (sister) for the presence of IgG antibodies against SARS-CoV-2 using an enzyme linked immunosorbent assay (ELISA) kit (EUROIMMUN, Luebeck, Germany); both tested negative.

Review of the literature

An electronic search was conducted on studies published from 1 December 2019 to 29 June by searching for the keywords 'covid-19' OR 'covid' OR 'SARS-CoV-2' AND 'neonate' on PubMed, MEDLINE, Google Scholar, medRxiv, and bioRxiv database. We also searched the references listed within the articles to identify additional articles that may have been missed during the electronic search. Eligible studies (including case reports, case series, cohort studies and retrospective studies) published in English-language journals that have described neonates diagnosed with COVID-19 were included for analysis. We summarized the studies involving neonates in Tables 2A and 2B [10,16–34]. Most of these neonates had an infected mother and were asymptomatic (n = 7) or became symptomatic after 16 h until 17 days after birth (n = 20).

They all recovered. To our knowledge, there is only one series report about neonates that showed viral loads (Ct values) in neonates. This report included 18 neonates and infants aged between 10–88 days old and showed extremely low values

Table 2A
Summary of studies of neonates with confirmed COVID-19.

Author	Han et al [10]. (n = 1)	Aghdam et al [16]. (n = 1)	Wang et al. [17]. (n = 1)	Zeng et al [18]. (n = 3)	Zhang et al [19]. (n = 4)	Coronado Munoz et al [20]. (n = 1)	Dumpa et al [21]. (n = 1)	Salik et al [22]. (n = 1)	Precit et al [23]. (n = 1)	Piersigilli et al [24]. (n = 1)	Paret et al [25]. (n = 1)	Alzamora et al [26]. (n = 1)
Gestational age (weeks)	38	Unknown	40	39, 39	>39	36	39	37	39	26 + 4	Unknown	33
Day of life when illness started	27 days	15 days	36 h	Unknown	30 h–17 days	21 days	22 days	7 days	10 days	7 days	25 days	16 h
Mode of delivery	Vaginal	CS	CS	CS	CS	Unknown	Vaginal	Unknown	Vaginal	CS	Unknown	CS
Presentation	Fever, cough, rhinorrhoea, feeding intolerance	Fever, feeding intolerance, mottling	Asympto-matic	Fever, cyanosis, feeding intolerance, dyspnoea	Fever, cough, feeding intolerance, dyspnoea	Rhinorrhoea, feeding intolerance, dyspnoea	Fever, feeding intolerance	Fever, dyspnoea, cyanosis, feeding intolerance, lethargy	Rhinorrhoea, dyspnoea	No COVID-19-related symptoms	Fever, irritability	Respiratory difficulty
Abnormal labs	/	None	Elevated CK and ASAT	None	/	Rhinovirus positive, elevated CRP and PCT	None	Elevated IgM, cytokine, and lymphocyte count	Low MCV and MCH	Leukopenia	/	None
Chest radiog-raphy	Normal	Normal	Abnormal	/	Abnormal	Bilateral infiltration	Normal	Bilateral pulmonary granular opacities	Bilateral ground glass opacities	Non-specific bilateral streaky infiltrates	Not performed	Normal
SARS-CoV-2 testing	PCR NP, stool, plasma, and urine	PCR NP	PCR NP	/	PCR NP and anal swabs	PCR NP	PCR NP	PCR NP	PCR NP, plasma, nares, and stool	PCR NP	PCR NP	PCR NP and plasma
Medication	None	Antibiotics, anti viral agents	Antibiotics	Antibiotics	Antibiotics	Antibiotics	Antibiotics	None	None	None	Antibiotics	None
Probable mode of transmis-sion	Horizontal	Horizontal	Vertical?	Horizontal	Horizontal	Horizontal	Horizontal	Horizontal	Horizontal	Vertical?	Horizontal	Vertical?
Outcome	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered

(Abbreviations: ASAT = Aspartate aminotransferase, CK = Creatine kinase, COVID-19 = coronavirus disease 2019, CRP = C-reactive protein, CS = sectio caesarea, GA = gestational age, MCH = mean cell hemoglobin, MCV = mean cell volume, NP = nasopharyngeal swab, PCR = polymerase chain reaction, PCT = procalcitonine).

Table 2B
Summary of studies of neonates with confirmed COVID-19.

Author	Diaz et al [27]. (n = 1)	Gregorio-Hernandez et al [28]. (n = 2)	White et al [29]. (n = 2)	Hu et al [30]. (n = 1)	Buonsenso et al [31]. (n = 1)	Patek et al [32]. (n = 1)	Chacon-Aguilar et al [33]. (n = 1)	Gordon et al. [34] (n = 1)
Gestational age (weeks)	38 + 4	38 + 1, 39	39, 39	40	38 + 3	39	Unknown	32
Day of life when illness started	8 days	2 days, 6 days	16 days, 25 days	36 h	15 days	14 days	26 days	4 days
Mode of delivery	CS	Vaginal	Vaginal, CS	CS	CS	CS	Unknown	CS
Presentation	Asymptomatic	Asymptomatic besides previous diagnosis	Fever, rhinorrhoea, hypoxia, conjunctivitis	Asymptomatic	Asymptomatic	Fever, fussiness, apnoea	Paroxysmal episodes, fever, rhinorrhoea, vomiting	Asymptomatic
Abnormal labs	None	Elevated CRP, PCT, lympho-cytopenia	Neutropenia, elevated CRP	Lymphocytosis	/	Elevated liver enzymes, neutropenia, monocytosis	Elevated CK and LDH	/
Chest radiography	Ground glass opacities	Consolidation lateral and posterior	Hazy opacities without consolidations	Normal	/	Bilateral perihilar streaking without focal consolidation	Not performed	Findings consistent with surfactant lung disease
SARS-CoV-2 testing	PCR NP	PCR NP	PCR NP	PCR NP	PCR NP	PCR NP	PCR NP, stool	PCR NP
Medication	None	None	None	None	None	Antibiotics, acyclovir	Antibiotics	None
Probable mode of transmission	Horizontal	Horizontal	Horizontal	Horizontal	Horizontal	Horizontal	Horizontal	Vertical?
Outcome	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered

(Abbreviations: ASAT = Aspartate aminotransferase, CK = Creatine kinase, COVID-19 = coronavirus disease 2019, CRP = C-reactive protein, CS = sectio caesarea, GA = gestational age, MCH = mean cell hemoglobin, MCV = mean cell volume, NP = nasopharyngeal swab, PCR = polymerase chain reaction, PCT = procalcitonine).

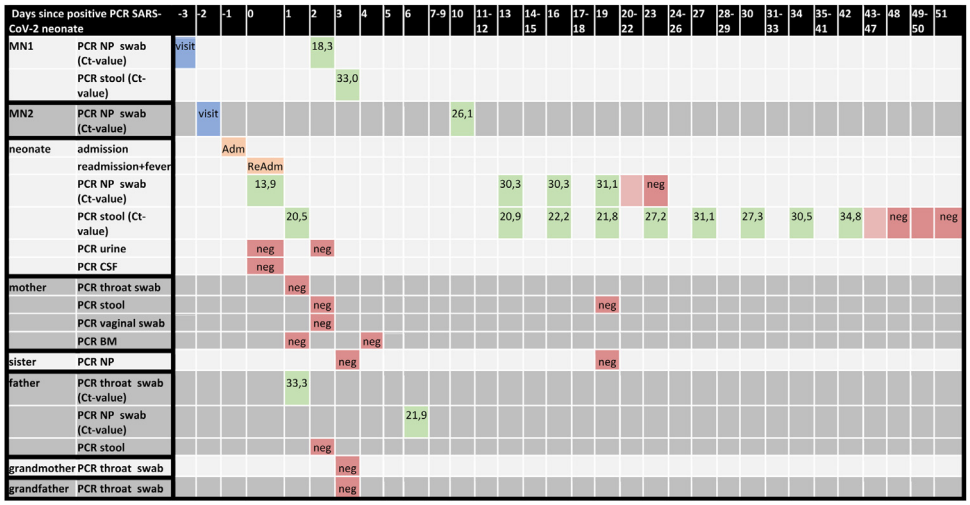

Fig. 1. Chronology of major epidemiological events and molecular testing results of neonate and close-contacts after positive PCR SARS-CoV-2 in neonate (Abbreviations: Adm = admission, BM = breast milk, CSF = cerebrospinal fluid, CT = cycle threshold values, MN = maternity nurse, neg = negative, NP = nasopharyngeal swab, PCR = polymerase chain reaction, ReAdm = readmission, SNP = single Nucleotide Polymorphisms, WGS = whole-genome sequencing).

between 3.00–6.58 [7]. Addiotionally, there are some case reports that report viral shedding in neonates. Gordon et al. reported the longest shedding of 28 days (nasopharyngeal swab) in a neonate [34]. Han et al. reported virus shedding in nasopharyngeal swab until day 17, stool until day 18, and urine until day 10 after onset of symptoms of a 27-day old neonate [10].

Discussion

We report a 7-day-old neonate with COVID-19 confirmed by PCR and with possible pyelonephritis. He had no respiratory or gastrointestinal symptoms. A high viral load of SARSCoV-2 RNA was found in nasopharynx and stool specimens and remained positive until day 42. The father, who had no clinical symptoms, and two maternity nurses who cared for the boy for one day only, were both positive for SARS-CoV-2 RNA and (one of them) probably infected this neonate. The mother had not previously been infected and was not infected by this neonate during the period of viral shedding despite the high viral load. As described in current literature, symptoms of COVID-19 in newborns were mild, or even none with complete recovery; which is consistent in our case report [7,10,16–34]. In most cases, the mother was infected and probably transmitted horizontally to the neonate. The mother in our case repeatedly tested negative for SARS-CoV-2 by PCR, and no IgG sero-reactivity was seen. Therefore, we conclude that the mother was not the source of this infection [35].

Literature shows SARS-CoV-2 incubation period are between 4–21 days [1–3,11]. This neonate became symptomatic 1.5 and 2.5 days after the visit of the maternity nurses. In this case, it is hard to determine the source of the infection. The neonate was born in the hospital and stayed for 1 day after birth, the father showed no symptoms and the maternity nurses showed symptoms 1 day after visiting this family. Sequencing showed all strains belonged to the same cluster. A relative fast incubation time could be possibly due to the high viral load of SARSCoV-2 RNA in our neonate. These Ct values are lower compared to children and adults [35–37]. Possible explanation include that neonates are presenting earlier in illness course than older people.

Viral shedding in different specimen types such as stool, urine, CSF, or blood remains uncertain in neonates. Limited data have shown that viral RNA could be detected in plasma or serum of neonates [10,22,25] and adult patients [37]. Just one case report detected viral RNA in urine of a neonate [10]. A recent review concluded that 3.7% of 430 adult patients were positive in urine [38]. We tested for SARS-CoV-2 RNA in urine, nasopharyngeal swab, stool, and CSF of the neonate, only nasopharyngeal swab and stool sample tested positive with prolonged virus shedding (Tables 2A and 2B). This is consistent with the current literature of children, PCR in stool was positive until 70 days in children [8,9,11,39,40,41]. The duration of viral shedding in neonates is scarce. Because of prolonged shedding in stool, it is necessary to be aware of the possibility of fecal-oral transmission of SARS-CoV-2 infection, especially in neonates and children.

Additionally, due to the relatively long duration of viral shedding, caution should be taken with diagnosis of COVID-19 in neonates and children presenting with COVID-19 like symptoms.

Currently, there is no consensus on infectivity during viral shedding [42,43]. Culture of live virus was not possible in our hospital. Wolfel et al. demonstrated that live virus SARS-CoV-2 can be cultured from nasal/throat and sputum samples in patients, however, no live virus was successfully isolated after day 8 from symptom onset despite ongoing high viral loads [43]. Bullard et al. investigated 90 SARS-CoV-2 RT-PCR confirmed positive samples and determined their ability to infect Vero cell lines. In this study, 28.9% demonstrated viral growth and they concluded that infectivity of patients with Ct >24 and duration of symptoms >8 days may be low [12]. Further research is needed to determine the viability of the virus outside and the duration of infectivity.

Conclusion

In conclusion, data of neonates with COVID-19 are very limited. This case report showed a neonate with a high viral load of SARS-CoV-2 and prolonged shedding with complete recovery. Thereby, only nasopharyngeal secretion and stool swab tested positive. Stool remained positive the longest until day 42. However, this course of infection is limited by this single case, additional data on COVID-19 infected neonates are necessary to confirm these findings. Until then, isolation of children or neonates with COVID-19 symptoms should be performed as soon as possible to prevent transmission to health care professionals and others.

Authors' contributions

MS and MV conceived the study, and participated in its design. MS and MV Drafted and revised the manuscript for content includ-

ing medical writing for content, analysis and interpretation of data. RB, SP, KG, BO conceived the study, participated in its design managed microbiology laboratory assays, and revised the manuscript. BO performed sequencing. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Included.

Availability of data and materials

Not applicable.

Competing interests

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jiph.2020.10.013.

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