Received: 27 June 2020 | Revised: 30 July 2020 | Accepted: 30 July 2020

DOI: 10.1111/ijlh.13318

LETTER TO THE EDITOR

ISLH International Journal of Laboratory Hematology WILEY

Gastrointestinal bleeding in a newborn infant with congenital factor X deficiency and COVID-19—A common clinical feature between a rare disorder and a new, common infection

Dear editor,

Congenital factor X (FX) deficiency is an extremely rare, bleeding disorder with an estimated incidence of one per 1 million. Patients with severe FX deficiency (FX:C < 1%) demonstrate a wide spectrum of serious clinical presentations, including hemarthrosis, hematoma, gastrointestinal (GI) bleeding, intracranial hemorrhage (ICH), and umbilical cord bleeding.[1] In fact, severe FX deficiency, with a high rate of life-threatening bleeding, is the second-most severe, rare coagulation factor deficiency (RCFD) after FXIII deficiency.[1,2] Although homozygotes are at risk of severe bleeding, heterozygotes usually are asymptomatic, but postsurgical bleeding or bleeding after childbirth may occur.[1,2] Other risk factors can increase the risk of bleeding in FX deficiency, and coronavirus disease 2019 (COVID-19), a new medical challenge, could affect the patient's bleeding or thrombotic tendency.[3] COVID-19, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presents an enormous challenge for everyone, especially for those with underlying risk factors such as cardiovascular disease, diabetes, obesity, and renal failure. Age and male sex are other risk factors.[4] Limited data are available regarding the effect of COVID-19 on patients with congenital bleeding disorders (CBDs), particularly RCFDs.[5] It has been shown that hypercoagulability-related adverse consequences are less common among patients with CBDs, at least in those with moderate-to-severe deficiency, but further studies, including our ongoing work on a large number of patients, are required.[5] Although there are several reports of newborns among infected pregnant mothers, this is the first report of such a case in an RCFD. This case report may help medical professionals to better manage similar cases. A 19-year-old pregnant woman was infected with SARS-CoV-2 early in the 9th month of pregnancy. Reverse transcriptase-polymerase chain reaction (RT-PCR) confirmed the infection. The patient had been in close contact with family members with confirmed COVID-19. The patient had cough and fever. Due to the mild presentation, she was given Azithromycin and advised to isolate herself at home. The symptoms resolved within 14 days. At end of her 9th month, three days prior to the planned cesarean section, she was rechecked for SARS-CoV-2 infection; her RT-PCR was negative. She successfully underwent cesarean section without complications and delivered a healthy full-term baby. Therefore, mother and newborn discharged the following morning. In the evening, the baby experienced bloody vomiting and was hospitalized for further assessment, which showed GI bleeding. At admission, laboratory tests showed a positive C-reactive protein (CRP) (qualitative), a low hemoglobin level, and prolonged prothrombin time (PT), and activated partial thromboplastin time (APTT) (Table 1). He was hospitalized in the neonate intensive care unit (NICU) for 10 days. Due to the risk of SARS-CoV-2 infection, on the third day after admission he was tested by RT-PCR, which was positive. The neonate received 30 mL frozen plasma (FFP) six times over 10 days, which resolved the GI bleeding. Tranexamic acid (TXA) was administered at a dose of 10 mg/kg every 8 hours. Due to lack of COVID-19 symptoms, he did not receive any special treatment for the disorder. After 10-day hospitalization in the NICU, the neonate was sent to an isolation room for 5 days, during which his condition stabilized, after which he was discharged in stable condition. He has had no complications during the past two months after discharge. Since the child's father and two other first-degree family members have severe FX deficiency, and the parents of the baby are closely related, the mother and the baby were checked for FX deficiency. Routine coagulation tests, and FX:C assay performed by STA Compact automatic coagulometer (Stago, Paris, France), revealed a severe deficiency in the baby, and a mild deficiency, compatible with heterozygote FX deficiency, in the mother (Table 1).

COVID-19 is an emerging medical challenge that can present more difficulties for those with special conditions, such as pregnant women and newborns. Due to alterations in cellular immunity, pregnant women are more prone to infection by intracellular pathogens like viruses.[6] The fetus is also highly susceptible to infection due to immaturity of the immune system.[7] Furthermore, the mother's (heterozygote) congenital coagulopathy and that of her newborn (homozygote) were additional potential risk factors, because a disrupted coagulation system is a prominent feature of SARS-CoV-2 infection.[8] To date, FX deficiency in a newborn has not been cited anywhere as a special condition requiring close attention in the case of SARS-CoV-2 infection. According to the few reports to date, SARS-CoV-2 infection is a risk factor for severe maternal morbidity. It is worth noting that most of those mothers were discharged without complications.[9] From a clinical aspect, fever was the most common symptom (68%) at the time of admission.[9] This was also observed in the affected woman of this study. SARS-CoV-2 infection can even affect the type of delivery. A systematic review of these women showed that about 92% of deliveries were by cesarean section, less than 10% being the usual vaginal delivery (7 of 85). Fetal distress was mentioned as the most

TABLE 1 Laboratory characteristics of mother and baby with factor X deficiency and COVID-19

Test	Proband (2nd day after birth)	Proband (7th day after birth)	Proband (2 months after hospital discharge)	Mother (about 3 1/2 months after SARS-CoV-2 infection)
WBC × 10^9/L	14.2 (8-24)[a,b]	9.43 (5-21)	10.79 (6-18)	8.7 (3.6-10.6)
RBC × 10^9/L	2.5 (4.36-5.96)	2.78 (4.2-5.8)	3.50 (3.4-5)	4.41 (3.8-5.2)
Hb (g/dL)	8.2 (16.4-20.8)	9.2 (15.2-20.4)	10.2 (10.6-16.4)	13.6 (12-15)
HCT (%)	24.6 (48-68)	27 (50-64)	29.2 (32-50)	41.4 (35-49)
Lymphocyte × 10^9/L	6.4 (1.3-11)	4.3 (1.2-11.3)	8.21 (2.5-13)	2.22 (1-3.2)
Neutrophil × 10^9/L	4.9 (2.6-17)	2.9 (1.5-12.6)	1.85 (1.2-8.1)	5.75 (1.7-7.5)
Platelet × 10^9/L	370 (150-450)	331 (150-450)	334 (150-450)	276 (150-450)
PT (sec)	>60 (PTC: 12.6)	90 (PTC: 12.6)	>60 (PTC: 10)	13 (PTC: 10)
APTT (sec)	>120 (APTTC: 31)	100 (APTTC: 30)	>120 (APTTC: 32)	37 (APTTC: 32)
CRP (Quantitative)	Trace	Negative	NC	NC
FX:C level	NC	NC	<1% (50%-150%)	40% (50%-150%)

Abbreviations: APTT, activated partial thromboplastin time; APTTC, APTT control; CRP, C-reactive protein; Hb, hemoglobin; HCT, hematocrit; NC, Not checked; PT, prothrombin time; PTC, PT control; RBC, red blood cell; WBC, white blood cell.

[a]Hematological test normal ranges are extracted from Rodak's Hematology: Clinical Principles and Applications, 5th Ed (2016).

[b]Normal values are placed in parentheses.

common indication for cesarean section. Our patient underwent a planned cesarean section, due to her previous history. The delivery itself was uneventful, and a healthy baby was delivered, while among other reported cases, a number of complications have been noted.[9] As with most other reports, the infant did not have any symptoms at the time of delivery and was discharged the day after birth.[9] In a case series of 10 patients, various first clinical presentations were observed, including shortness of breath (n = 6), fever (n = 2), vomiting (n = 1), and rapid heart rate (n = 1).[10] In the case at hand, bloody vomiting was the first clinical presentation. In the same case series, one died due to refractory shock, multiple organ failure (MOF), and disseminated intravascular coagulation (DIC). Another patient with severe presentation was managed by intravenous infusions of gamma globulin, platelets, and plasma, which was suggestive of the effectiveness of gamma globulin in severe cases. The author recommended early use of intravenous gamma globulin for passive immunization.[10] GI bleeding in our case was successfully managed by administration of FFP and TXA. In addition to thrombotic complication, bleeding is not infrequent in patients affected by COVID-19, with GI bleeding seemingly the most common hemorrhagic manifestation among adults. GI bleeding, with a frequency of 40%, was observed among neonates from affected mothers.[3] On the other hand, GI bleeding is also a relatively common presentation among severely FX deficient patients.[1,2] In fact, GI bleeding can occur in children with severe FX deficiency within the first months of life. It seems that such patients are prone to experience severe bleeding, such as ICH, later in life, in the absence of an appropriate therapeutic strategy, most likely preventative regular secondary prophylaxis.[1,2] In one study of 102 patients with congenital FX deficiency, GI bleeding has been reported in 12% of symptomatic cases.[1] In this case, with GI bleeding being a common presentation of SARS-CoV-2 infection and congenital FX deficiency, it cannot definitively be attributed to one or the other. Close monitoring of such cases is necessary to decrease related adverse consequences. Although it seems that COVID-19 is less severe in adults with CBDs, it is a less-known issue among children and newborns with CBDs. Further reports and studies could provide clarity. Due to their severe bleeding tendency, close monitoring of patients with severe congenital FX deficiency is mandatory, even without potential SARS-CoV-2 infection. And close monitoring of neonates with infected mothers is mandatory to prevent severe consequences. Patients with concomitant infection with SARS-CoV-2 require even more rigorous preventative and supportive care.

KEYWORDS

COVID-19, factor X deficiency, gastrointestinal bleeding, rare bleeding disorders

ACKNOWLEDGEMENTS

We highly appreciate Daisy Morant's valuable aid in improving the English Language of this manuscript. The study was supported and approved by Shahid Beheshti University of Medical Sciences.

CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

A. Dorgalaleh designed the work, performed laboratory analysis, and wrote the manuscript. F Ghazizadeh, M. Baghaipour, A. Dabbagh, Gh. Bahoush, and N Baghaipour performed clinical studies. Sh. Tabibian, M. Jazebi, N. Baghaipour, M. Bahraini, A. Fazeli, and F. Yousefi performed laboratory analysis. All the authors approved the submission.

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