Letter to the Editor

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Is COVID-19 a hyperferritinemic syndrome in children?

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To the Editor,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is hallmarked by hyperinflammatory cytokine storm causing far more morbidity and mortality than from any direct viral cytotoxicity [1]. Once evading the respiratory system, SARS-CoV-2 induces an immune and inflammation reaction resulting in increased expression of interleukin (IL) 6, IL8, IL10, TNF- α , monocyte chemoattractant protein-1, C-reactive protein (CRP), and ferritin [2]. In hospitalized adults with Coronavirus disease 2019 (COVID-19), ferritin serum levels were found significantly correlated with disease severity [3]. The prevalence and the significance of high ferritin levels in children with COVID-19 are poorly investigated. We described clinical presentation, laboratory evaluation, and outcome in pediatric patients with SARS-CoV-2 infection according to ferritin levels.

We retrospectively enrolled all pediatric patients (aged <14 years) with laboratory-confirmed SARS-CoV-2 infection admitted to a Tertiary Care Pediatric Hospital (Campania region, Italy) from October 14, 2020 to February 28, 2021. This hospital has been identified as the Regional Spoke for

diagnosis of children's SARS-CoV-2 infection. Data on demographics, exposure history, medical history, clinical presentations, laboratory tests, imaging investigation, and treatments were collected. Laboratory investigation at admission included complete blood count, inflammatory markers (at least one or both among CRP, and procalcitonin [PCT]), liver functional tests, electrolytes, general biochemical exams, and ferritin (electrochemiluminescence immunoassay, Roche; reference values according to patient's age and sex: both sex ≤ 1 year 320 ng/mL, both sex >1 and <6 years 6–67 ng/mL, female ≥ 6 years 7–84 ng/mL, male ≥ 6 years 14–150 ng/mL). In a subgroup of patients, evaluation of serum IL2 receptor (IL2r) (immunometric test; reference value 223–710 IU) and IL6 (electrochemiluminescence analysis, reference value 0–5 pg/mL) was also performed.

Only patients with complete medical chart reviews and availability of laboratory results including ferritin values were included in the analysis. Patients with criteria fulfilling a multisystem inflammatory syndrome COVID-19-related (MIS-C) were excluded from the study. All hospitalized patients received the same diagnostic and treatment protocols. Confirmation of SARS-CoV-2 infection was obtained by real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2 nucleic acids on nasal and oropharyngeal swabs. RT-PCR was performed at our local reference laboratory. Statistical analysis was performed on StataCorp LLC Stata 13.0 (College Station, TX). Medians, interquartile ranges for continuous variables and numbers, percentage for categorical variables were used. Categorical variables were evaluated with chi-square test and Fisher's test. Wilcoxon's rank sum test was used for continuous variables. A p-Value <0.05, two tailed, were considered statistically significant.

Overall, 76 hospitalized patients with confirmed SARS-CoV-2 infection were included. All patients were symptomatic at admission. Basic characteristics of patients are reported in Table 1. Family clustering was the major transmission route of SARS-CoV-2 in our cohort. Eleven (14%) children had an underlying medical condition: severe neurological disease in three cases, kidney disease in two patients, chronic respiratory condition in two cases, congenital heart disease in two patients, prematurity in

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Table 1: Demographic, clinic and laboratory parameters at baseline in 76 hospitalized pediatric patients with COVID-19.

Parameters	Values
Male ^a	45 (59%)
Age in months ^b	3 (1–13)
Epidemiologic link to persons with a definitive SARS-CoV-2 infection ^a	39 (52%)
Underlying conditions ^a	11 (14%)
Clinical presentation: ^a	
Fever	57 (75%)
Pharyngitis	3 (4%)
Cough	7 (9%)
Dyspnea	2 (3%)
Headache	1 (1%)
Abdominal pain	1 (1%)
Diarrhoea	15 (20%)
Inappetence	17 (16%)
Vomiting	6 (8%)
Other	14 (18%)
Duration of symptoms before hospital admission in days ^b	1 (1–2)
Duration of hospital stay in days ^b	2 (1–4)
Laboratory investigation at baseline:	
WBC count/ μ L ($\times 1,000$) ^b	7.6 (5.6–11.4)
Lymphocytes count/ μ L ($\times 1,000$) ^b	3.5 (2.2–6.1)
Platelet count/ μ L ($\times 1,000$) ^b	320 (272–421)
AST, IU/L ^b	37 (31–51)
ALT, IU/L ^b	25 (16–33)
LDH, U/L ^b	542 (490–586)
CRP, mg/L ^b	1.42 (0.64–5.39)
Patients with CRP above the normal value ^a	23 (30%)
PCT, ng/mL ^a	0.12 (0.08–0.17)
Patients with PCT above the normal value ^a	23 (32%)
Patients with ferritin above the normal value ^a	30 (39%)

^aNumber (%). ^bMedian (interquartile range). WBC, white blood cells; AST, aspartate aminotransferase (n.v. 5–58 units/L); ALT, alanine aminotransferase (n.v. 8–40 units/L); LDH, lactate dehydrogenase (n.v. 300–550 units/L); CRP, C-reactive protein (n.v. 0.0–5.0 mg/L); PCT, procalcitonin (n.v.: 0.0–0.5 ng/mL); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

one case, and biliary atresia in one infant. Fever was the most common symptom (70%), followed by gastrointestinal symptoms (diarrhea, inappetence, and vomiting). Very few patients had a lower respiratory tract involvement. As for laboratory investigation, nitrogen test, creatinine, albumin, and coagulation function test including fibrinogen were normal in all cases. Forty-six (61%) patients had normal ferritin value, according to reference values for age and sex above mentioned (Group 1, “normal ferritin”), while in 30 (39%) cases ferritin was higher than the reference value for age and sex (Group 2, “high

Table 2: Characteristics of patients divided in two groups according to ferritin levels.

Parameters	Group 1 “Normal ferritin”	Group 2 “High ferritin”	p- Value
Number of patients ^a	46	30	–
Males ^a	33 (72%)	12 (40%)	0.01
Age in months ^b	9 (3–23)	1 (0–3)	0.01
Epidemiologic link to persons with a definitive SARS-CoV-2 infection ^a	23 (51%)	16 (53%)	0.85
Underlying conditions ^a	9 (20%)	2 (7%)	0.12
Clinical presentation ^a			
Fever	32 (70%)	25 (83%)	0.18
Pharyngitis	3 (7%)	0 (0%)	0.15
Cough	4 (9%)	3 (10%)	1.00
Dyspnea	1 (2%)	1 (3%)	1.00
Headache	1 (2%)	0 (0%)	1.00
Abdominal pain	1 (2%)	0 (0%)	1.00
Diarrhoea	6 (13%)	9 (30%)	0.07
Inappetence	6 (13%)	8 (27%)	0.13
Vomiting	5 (12%)	1 (3%)	0.21
Other	10 (22%)	4 (13%)	0.36
Duration of symptoms before hospital admission in days ^b	1 (1–2)	1 (0–2)	0.60
Duration of hospital stay in days ^b	2 (1–3)	2 (2–5)	0.86
Laboratory investigation at baseline:			
WBC count/ μ L ($\times 1,000$) ^b	7.6 (5.6–11.4)	7.4 (6.3–10.0)	0.81
Lymphocytes count/ μ L ($\times 1,000$) ^b	3.5 (2.2–5.8)	3.4 (2.0–6.3)	0.96
Platelets count/ μ L ($\times 1,000$) ^b	320 (272–410)	334 (293–459)	0.67
AST, IU/L ^b	30 (36–45)	45 (36–64)	0.05
ALT, IU/L ^b	22 (14–27)	29 (20–38)	0.02
LDH, U/L ^b	523 (487–585)	554 (492–586)	0.06
CRP, mg/L ^b	1.61 (0.63–8.9)	1.35 (0.65–2.65)	0.64
Patients with CRP above the normal value ^a	18 (39%)	5 (17%)	0.04
PCT, ng/mL ^b	0.12 (0.07–0.16)	0.13 (0.11–0.18)	0.23
Patients with PCT above the normal value ^a	3 (7%)	1 (3%)	1.00
Treatments: ^a			
Antibiotics	8 (19%)	10 (36%)	0.12
Oral steroids	3 (7%)	9 (32%)	0.01
Fluid therapy	5 (12%)	6 (21%)	0.28

^aNumber (%). ^bMedian (interquartile range). WBC, white blood cells; AST, aspartate aminotransferase (n.v. 5–58 IU/L); ALT, alanine aminotransferase (n.v. 8–40 IU/L); LDH, lactate dehydrogenase (n.v. 300–550 U/L); CRP, C-reactive protein (n.v. 0.0–5.0 mg/L); PCT, procalcitonin (n.v.: 0.0–0.5 ng/mL); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

ferritin”). In Group 2, ferritin mean times upper the reference value were 2.17 ± 1.15 . When characteristics of patients were analyzed according to ferritin levels (Group 1 vs. Group 2), we found that patients belonging to the Group 2 were significantly younger than those of Group 1 (Table 2). Clinical presentation did not significantly differ between the two groups. No patient showed organomegaly. Only one patient (a girl of 12 months) had a severe onset of SARS-CoV-2 infection, hypovolemic shock and severe dyspnea. She received mechanical ventilation for 1 day, followed by non-invasive ventilation other 4 days. Her chest X-ray showed ground-glass opacity. Although the severe clinical picture, patient had a slightly increased ferritin levels (448 ng/mL; 1.4 times upper the normal reference value) and she completely recovery within 12 days. As for laboratory results, patients in Group 2 have significantly higher transaminases values compared to those in Group 1. In seven (23.3%) patients of the Group 2 serum IL2r and IL6 dosage were available. We found levels above the reference value in all of them (median IL2r value $2,851.6 \text{ IU} \pm 897.1$, normal range 223–710; median IL6 value $10.3 \text{ pg/mL} \pm 7.9$, normal range 0–5). Unfortunately, we did not perform IL dosage in Group 1. As for treatments, fluid therapy was administered in 11 (14.5%) patients. Eighteen (23.7%) patients received antimicrobials. Twelve (15.8%) patients received oral steroids. Patients belonging to Group 2 received more frequently oral steroids compared to patients of Group 1 ($p=0.01$). No death was observed in our cohort of patients.

To our knowledge, this is the first study evaluating serum ferritin in a large group of children with COVID-19. The results of laboratory tests of children with COVID-19 were more often within the normal range than those of adults [4, 5]. These data are confirmed in our study. No significant disorders were observed in the functions of the kidney, liver, LDH levels, and myocardial enzymes in our cohort. This could be related to the benignity of COVID-19 in pediatric population. However, very few reports investigated ferritin levels in children with SARS-CoV-2 infection [4]. Ferritin is a biomarker not only in iron-related disorders but also in inflammatory diseases, or diseases in which inflammation has a central role such as cancer, neurodegeneration, or infection [6].

Ferritin is not only regulated by inflammatory stimuli, but can also function as the enhancer of the inflammatory response increasing expression of several proinflammatory mediators [6]. The inflammatory reaction is a critical part of the host immune response to the presence of microbial pathogens. High ferritin levels have been reported in viral infection as HIV [7]. A correlation between high serum ferritin, decreased CD4+ T cell numbers and mortality has been also reported [7]. Not all viral infections are associated

with increased ferritin levels. In contrast with HIV, patients infected with hepatitis B or hepatitis C virus do not exhibit increased ferritin levels, consistent with a lower stimulation of the inflammatory response [7]. On the bases of the link between ferritin and inflammation, not surprisingly, high levels of ferritin have been reported in patients with COVID-19. In adults with SARS-CoV-2 infection, high ferritin has been found mainly in patients with a more pronounced inflammatory response and a poor outcome [3]. While the identification and treatment of hyperinflammation are mandatory in adults with acute SARS-CoV-2 infection and in children with MIS-C [8], the role of high ferritin levels in infants with a mild COVID-19 disease is not fully clear. It is to note that our single patient with a severe presentation had a slightly increased ferritin, suggesting that even in pediatric age there is an inter-individual difference in the activation of the SARS-CoV-2-related inflammatory cascade. If the clinical course of patients with elevated ferritin was mild because of steroids therapy or because of the benign characteristics of SARS-CoV-2 infection in children is to demonstrated. To support the hypothesis of a SARS-CoV-2-induced systemic inflammation in patients with elevated ferritin, we found high IL levels (both IL2r and IL6) in patients of Group 2. These cytokines (mainly IL6) are high in adults with a severe COVID-19 [2]. Unfortunately, it was not possible to measure other cytokines in our laboratory.

In conclusion, infants with SARS-CoV-2 infection may present a systemic hyperinflammation documented by high serum ferritin. Differently from adults, elevated ferritin in these patients seems not to be related to a more severe clinical course or poor outcome. Further clinical studies are needed to confirm our observation and to clarify the significance of ferritin in mild symptomatic children with acute SARS-CoV-2 infection. Interleukins as IL2r and IL6 should be also investigated in order to find a correlation with hyperferritinemia and a more severe course of COVID-19 in infants.

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