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A Comprehensive Update of ICET-A Network on COVID-19 in Thalassemias: What We Know and Where We Stand

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Summary. A review of the literature on COVID-19 pandemic in patients with thalassemias is presented. Globally, the prevalence of COVID-19 among β-thalassemia patients seems to be lower than in general population; associated co-morbidities aggravated the severity of COVID- 19, leading to a poorer prognosis, irrespective of age. A multicenter registry will enhance the understanding of COVID-19 in these patients and will lead to more evidence-based management recommendations. (www.actabiomedica.it)

Key words: COVID-19 pandemic, thalassemias, iron overload, associated co-morbidities, clinical outcome, update

Background

β-thalassemias are a group of hereditary blood disorders characterized by defects in the synthesis of the β chains of hemoglobin A, resulting in variable phenotypes ranging from severe anemia to clinically asymptomatic individuals (1). Globally, it is estimated that there are 270 million carriers with abnormal hae-

moglobins and thalassemias, of which 80 million are carriers of β-thalassemia. Recent surveys suggest that between 300,000 and 400,000 babies are born with a serious hemoglobin disorder each year (23,000 with transfusion-dependent thalassemia; TDT) and that up to 90% of these births occur in low- or middle-income countries (2).

Clinically, β-thalassemias can be classified as TDT and non-transfusion-dependent thalassemia (NTDT) according to the severity of the clinical phenotype, which basically depends on the broad spectrum of β-thalassemia mutations that can be found in a homozygous or compound heterozygous state.

Current treatment of TDT consists of regular transfusions, (at 2-4 week intervals), that lead to iron overload, requiring iron chelation to prevent organ toxicity. NTDT patients are not, in general, dependent on transfusions, except occasionally; however, in the long-term they do develop iron overload because of ineffective erythropoiesis and increased intestinal iron absorption (3).

In the last six months, healthcare systems worldwide have been facing a novel viral disease. The highest infection rate occurs in adults; however, neonates, children, and adolescents are also infected. The infection by SARS-CoV-2 in individuals is characterized by a wide spectrum of clinical symptoms, from asymptomatic to those with mild symptoms (81% of patients), and a small proportion of patients with fatal outcome. Fourteen percent of infected people have a severe illness requiring hospitalisation and supplemental oxygen, and the remaining 5% become critically ill with respiratory failure, septic shock and/or multi-organ dysfunction. Recent estimates of COVID-19 case fatality rates are around 2%, rising to 15% in patients aged 80 years or over (4).

In patients with thalassemias, several factors could predispose for an increased risk for acquiring COVID-19 and consequent complications, including frequent hospital visits and admissions (5-7).

Here, we provide a brief review of the literature of the first 6 months of the COVID-19 outbreak in patients with thalassemias. Any relevant articles that reported clinical characteristics and epidemiological information on infected patients were included in the update.

Literature search

We carried out a systematic literature search, from 1 January 2019 to 17 June 2020, using the main online databases (PubMed, Google Scholar, and MEDLINE) with the following keywords: 'COVID-19', '2019-nCoV', 'coronavirus' and "Thalassemias", 'coronavirus' and "Hemoglobinopathies".

First clinical report

According to COVID-19 webinar presented by the European Hematology Association, 51 patients with TDT and COVID-19 have been reported from 9 countries (https://ehaweb.org/covid 19/ webinars. Session 3; April 16th, 2020). Most of them presented with mild to moderate respiratory symptoms (46 out of 51) and 3 out of 5 hospitalized patients died.

Second clinical report

A small cohort of 10 TDT and 1 with NTDT patients from Northern Italy, (6 females and 5 males), experienced COVID 19 disease (8). One patient with TDT had pulmonary hypertension treated with sildenafil and 8 were splenectomised. The likely source of infection was detected in 55% (6/11) of cases: 2 had contacts with COVID-19 positive subjects, and 4 had occupational exposure. Three patients were asymptomatic and one TDT patient, with a history of diffuse large B-cell lymphoma treated with chemotherapy and currently in complete remission, was admitted with high fever and bone marrow hypoplasia, lymphopenia, and agranulocytosis while on treatment with deferiprone. 6/11 were hospitalized, but none required mechanical ventilation. The clinical course ranged from 10 to 29 days (8).

Third clinical report

A multicenter, retrospective cross-sectional study was conducted across all comprehensive thalassemia centers in Iran, from January to April 2020. All sus-

pected and confirmed COVID-19 cases were reported, from a total of 15,950 TDT and 2,400 NTDT patient who were registered by the Iranian Ministry of Health. Fifteen confirmed cases of COVID-19 (12 in TDT and 3 in NTDT) were reported. Concomitantly, 8 symptomatic patients with β-thalassemia (6 TDT and 2 NTDT) who were suspected as having COVID-19 were also reported. The mean age of confirmed and suspected patients was 36.1 ± 12.1 (range: 22-66) and 39.6 ± 9.03 (range: 30-54) years, respectively. More than 60% in each group (TDT and NTDT) had at least one comorbidity consisting of insulin-dependent diabetes, heart disease, pulmonary artery hypertension, hypertension due to renal dysfunction, osteoporosis, history of hepatitis C (HCV) positivity, liver disease, and asthma. Frequency of patients with at least one major underlying disease was 41.7% in TDT and 100% in NTDT (p: 0.123). Serum ferritin levels were above 2,000 ng/ml in 21.4% of the RT-PCR positive and 42.9% in suspected not-tested group (9).

Eleven patients had mild to moderate symptoms and recovered, and four confirmed severe cases, with at least one comorbidity, died. The minimum age for disease occurrence and death was 22 and 30 years in the confirmed COVID-19 patients with TDT, and 30 and 34 years in the suspected cases.

Fever and cough were the most prevalent symptoms at disease onset in both deceased patients and recovered patients. Other prevalent symptoms at onset of illness, in deceased patients, were fatigue, dyspnoea, chest tightness, and sputum production; few had anorexia, diarrhoea, and myalgia. Dyspnoea and chest tightness were much more common in deceased patients than in recovered patients. Hydroxychloroquine combined with lopinavir/ritonavir or atazanavir were the suggested treatment regimens (9).

In summary, this was the first nationwide survey that systematically evaluated the prevalence of COVID-19, the presence of comorbidities and the prognosis in patients with TDT and NTDT living in Iran. The prevalence of coronavirus disease in the general Iranian population was 11.01 per 10,000 and in patients with β-thalassemias 8.17 per 10,000 population (p: NS). Mortality rate of coronavirus disease was significantly higher in patients with β-thalassemias (26.6%) compared to the general population (6.34%) (p: 0.001) (9). In patients with TDT, suboptimal treatment or poor compliance to iron chelation therapy is associated with multiple organ damage, including pancreas (insulin-dependent diabetes), heart failure or arrhythmia and chronic liver disease, whereas due to the basic pathophysiology of the disease, hypercoagulable state and pulmonary hypertension are more common in NTDT patients (10).

Fourth clinical report

An International Multicentre Study (IMS), promoted by the International Network of Clinicians for

Endocrinopathies in Thalassemia and Adolescence Medicine (ICET-A) retrospectively investigated the epidemiological, clinical and therapeutic aspects of SARS-CoV-2 infection in 4,962 patients with TDT and 1,289 patients with NTDT, followed in 17 Centers in 10 different countries. The preliminary results were: 10 COVID-19 patients (3 confirmed asymptomatic and 7 symptomatic), with a ratio of males/females 3/7 and a mean age 35.7±11.7 (range 22-66) years. Experimental treatments for COVID-19 included hydroxychloroquine, azithromycin/clarithromycin or moxifloxacin. Low molecular weight heparin and antiviral drugs were less commonly used. The outcome of COVID-19 was moderate in five patients and severe in a 30 year-old female with TDT, who developed critical COVID-19, followed by death in an Intensive Care Unit (10).

Fifth clinical report

A national UK survey of confirmed and suspected COVID-19 cases in 195 patients with haemoglobinopathies and rare anaemias (84% with SCD, 10.2 TDT, 2.5% NTDT, and 3.1% rare anaemias) was presented by Telfer et al. to HEA on 13 June 2020 (https://library.ehaweb. org/eha/ 2020/eha25th/303394). A total of 195 cases (male: 86; female: 109) were reported.

The median age was 33 years. There were 175 adults and 20 children (≤18 years). PCR for SARS-CoV-2 RNA was positive in 98 of 154 (64%) cases

tested. Two patients who died, 1 with TM and 1 with TI, had comorbidities.

The general available patients' characteristics and the clinical manifestations observed in thalassemic patients with confirmed COVID-19 reported in the literature are summarized in tables 1 and 2.

An uncommon presentation in an adolescent

A 17-y-old girl with TDT presented with acute loss of sense of smell (anosmia) and diminished sense of taste (ageusia) 8 days prior to admission, and history of sneezing in the prior 2 days. Oropharyngeal swab tested for SARS-CoV-2 was positive, chest X-ray was normal, and serum ferritin level was 980.51 ng/ml. Laboratory studies showed low hemoglobin level (7.5 g/dl), normal white blood cell count (9.4×10^3/μL), with 54.9% neutrophils and 34.2% lymphocytes, prothrombin time prolongation (PT: 14.5 s; normal APTT: 31.6 s), hyperuricemia (6.3 mg/dl), and increase of C-reactive protein level (6 mg/dl). Supportive and therapeutic treatment consisted of blood transfusions, antibiotic (Azithromycin: 500 mg/q 24h) and antiviral (Oseltamivir: 75 mg/q 12h). Three days after hospital admission, she complained of mild-moderate muscle aches, which were relieved by using Paracetamol. Iron chelation therapy was not stopped considering her good clinical condition. The follow-up of anosmia and ageusia was not reported (11).

Table 1. Demographic, clinical and laboratory variables in 3 studies of thalassemic patients with confirmed COVID-19

Clinical and laboratory variables	Motta et al. (Ref. 8)	Karimi M et al. (Ref. 9)	De Sanctis V et al. (Ref.10)
Clinical phenotype: TM and TI	10/1	12/3	8 /2
Gender male (M) / female (F)	5/6	7/8	3 /7
Age in yrs, mean± SD and range	44 ±11 (31-61)	36.1 ± 12.1 (22-66)	35.7±11.7 (22-66)
Body mass index (Kg/m²)	1 Obese	NR	19.39 ± 3.5
Household or community exposure	6/11	NR	4/10
Hospitalization in symptomatic patients	6/11 (5 in low-intensity care unit and 1 in high-intensive care Unit)	Not fully reported	4/10 (3in low-intensity care unit and 1 in high-intensive care Unit)
Splenectomy	8/11	12/15	4/10
Presence of comorbidities	6/11	8/15	5/10
LIC: MRI T2* (mg Fe/g d.w.)	Mild: 1/11; Severe 1/11	NR	Mild: 3/10; Moderate 2/10; Severe 3/10
Myocardial T2* (ms)	1/11 6.47 ms	NR	6/10 >20 ms; 1/10: 16 ms
Last serum ferritin level mean±SD (ng/ml, range)	1,716.3±1,468.9 (410-5,000)	1,725 ± 2,245 (225-8,200)	1,653 ± 1,592 (225-5,960)
Iron chelation and other treatment prior COVID-19	DFP: 3/10; DFX: 6/10; DFO-DFX: 1/10	NR	DFO: 3/10; DFP:1/10; DFX: 6/10; DFO-DFX: 1/10; HU: 4/10

Legend = TM: β -thalassemia major; **TI**: β-thalassemia intermedia; **NR:** Not reported; **LIC:** liver iron concentration, was classified as mild (LIC > 3 and < 7), moderate (LIC > 7 and < 14) and severe (LIC > 14 mg/g/d.w.); **HCV Ab:** hepatitis C antibodies; **Myocardial T2* value:** normal >20 ms, mild to moderate iron overload:10 -20 ms and severe : <10 ms; **DFO:** desferrioxamine; **DFP:** deferiprone; **DFX:** deferasirox, **HU:** hydroxyurea

Table 2. Clinical manifestations in 3 studies of thalassemic patients with confirmed symptomatic COVID-19

Clinical manifestations	Motta et al. (Ref. 8)	Karimi M et al. (Ref. 9)	De Sanctis V et al. (Ref.10) (*)
Fever	9/11	10/15	5/7
Tachypnea/dyspnea	NR	NR	4/7
Cough	10/11	9/15	7/7
Rhinorrhea	NR	1/15	2/7
Pharyngeal erythema	NR	NR	3/7
Conjunctivitis	NR	NR	2/7
Headache	NR	NR	6/7
Diarrhea	2/11	NR	2/7
Fatigue	1/11	NR	6/7
Vomiting	NR	NR	2/7
Abdominal pain	NR	NR	0/7
Anosmia/hyposmia	6/11	1/10	3/7
Ageusia	6/11	NR	NR
Oxygen saturation <93%	NR	NR	2/7
Death	0/11	4/15	1/7

Legend: * 3 patients were asymptomatic**; NR:** Not reported.

We have limited data on the significance of anosmia and ageusia in SARS-CoV-2 infection in children and adolescents (12). In a series reported by Mao et al. (13) analyzing the neurological manifestation of 214 COVID-19 in adult patients, hypogeusia occurred in 5.6% of patients, whereas 5.1% reported hyposmia.

Smell and taste disorders are related to a wide range of viral infections (13,14). Damage to the olfactory nerve during invasion and multiplication of SARS-CoV-2 may explain anosmia observed in the early stage of COVID-19 (12). Ageusia may be a secondary result of olfactory dysfunction. Moreover, the angiotensin-converting enzyme 2 receptor, which is the main host cell receptor of SARS-CoV-2 for binding and penetrating cells, is widely expressed on epithelial cells of the oral mucosa (15). Damage to mucosal epithelial cells of the oral cavity may explain ageusia observed in the early stage of COVID-19. Most adult patients with anosmia or ageusia have recovered within 3 weeks (16).

General recommendations

The advice for early and vigilant monitoring, along with high quality supportive care, in thalassemic patients at high risk for SARS-CoV-2 infection, was first given by the Thalassemia International Federation (TIF) (17), Vives Corrons and De Sanctis (18), and Karimi and De Sanctis (7). The latter authors also gave a descriptive analysis of potential risk factors in patients with thalassemias. In particular: blood transfusion, iron overload and oxidative stress, iron chelation and splenectomy, chronic liver disease, cardiac complications, diabetes and adrenal insufficiency, and defective immune response. They concluded that a multicenter registry and a collection of comprehensive data from both TDT and NTDT patients with positive COVID-19 are necessary to clarify debated issues and avoid under-reporting of mildly affected or symptomless patients not presenting to the health centres.

Current COVID-19 therapy involves treatment of symptoms, supportive care and prevention of complication, but no targeted medication. Therefore, the best strategy remains prevention. In spite of limited clinical evidence, in the last two months some general recommendations have been made for subjects with hemoglobin disorders (19,20).

Patients' concerns

Many patients with thalassemia and their families are concerned or distressed about the impact of COVID-19 in regard to isolation, blood supply sufficiency and safety (6), management of endocrine complications (diabetes, hypocortisolism, hormone replacement therapy), emotional stress , anxiety, delay in specialist consultations, and others (De Sanctis V, personal experience). It is thus vital that the information they receive is accurate, consistent, and up to date, especially in the light of incorrect or incomplete information that circulates widely on social media. Clinicians should also protect vulnerable patients and promote wellbeing during the pandemia.

Conclusions

Currently, the research on COVID-19, with its broad spectrum of severity, is growing at great speed, since its initial identification. To date, only one study has been conducted on the prevalence of COVID 19 in thalassemia compared to the general population (9). The youngest patient was 22 years (9,10). Most patients developed mild to moderate disease and recovered, though multiple comorbidities predisposed some of them to a severe disease (9,10). No definite conclusions regarding the prevalence of infection compared to the general population can be made in patients with thalassemia based on the current limited evidence and the lack of national registries. Although the pathophysiological mechanisms are still not well understood, it has been observed that most severe and fatal cases with COVID-19 have occurred in patients with underlying comorbidities (9). The youngest reported age of deceased patients was 30 years. Therefore, there is an urgent need for basic and clinical investigations to address factors which may adversely affect these patients in the face of Covid-19.

Measures to reduce the risk of disease in thalassemia patients should be implemented, guided by the local ministries of health and experts in the field of hemoglobinopathies.

The COVID-19 pandemia is having a profound effect on patients' mental and physical health. Therefore, actions are needed, in vulnerable patients, to mitigate the impact of COVID-19 on mental health by protecting and promoting their psychological wellbeing.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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