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Implications of SARSr-CoV 2 infection in thalassemias: Do patients fall into the "high clinical risk" category?

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Summary. We're all flying blind regarding coronavirus, but it's fair to think if thalassemic patients are particularly vulnerable to SARS-COV-2 infection or are at potential higher risk of complications from COVID-19 than normal population, specially when they become older. The frustrating thing is that, right now, this virus is still new. It only came to the attention of the World Health Organization at the end of December. Very few cases in thalassemia have so far been reported; is this due to lack of testing or a true lack of infection/susceptibility? However, we believe that more data should be collected to better characterise the impact of SARS-CoV-2 infection in patients with thalassemias. Therefore, a multicenter registry and the collection of comprehensive data from both positive COVID-19 thalassemia major and non-transfusion dependent thalassemia are necessary to clarify debated issues. In the meantime an early and vigilant monitoring along with high quality supportive care are needed in thalassemic patients at high risk for SARS-CoV-2 infection. (www.actabiomedica.it)

Key words: Thalassemia, SARS-COV-2 infection, Covid-19, risk factors

Background

The world has experienced two outbreaks of highly pathogenic Coronaviruses (CoVs), including the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, with 8,422 people infected and 916 deaths worldwide, the epidemic Middle East Respiratory Syndrome coronavirus (MERS-CoV in 2012) in 2012, with a total of 1,401 people infected and 543 deaths.

In December 2019 a new strain of coronavirus, officially named severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), was first isolated from three patients with coronavirus disease 2019 (COVID-19) by the Chinese Center for Disease Control and Prevention (1,2).

The genetic sequence of the COVID- 19 showed more than 80% identity to SARS-CoV and 50% to the MERSCoV, and both SARS-CoV and MERS-CoV originate in bats (3).

SARS-CoV-2 has four major structural proteins: the spike surface glycoprotein, small envelope protein, matrix protein, and nucleocapsid protein (4,5). The spike protein binds to host receptors via the receptor-binding domains (RBDs) of angiotensinconverting enzyme 2 (ACE2) (6). The ACE2 protein has been identified in various human organs, including the respiratory system, gastrointestinal tract, lymph nodes, thymus, bone marrow, spleen, liver, kidney, and brain (7).

Recent studies have shown that the novel coronavirus SARS-COV-2 binds to ACE2 receptors on target cells through the RBD on viral particles, leading to replication (6).

Epidemiological reports have provided evidence for person to person transmission of the SARS-Cov-2 in family and hospital settings. The symptoms of COVID-19 are not specific, which makes it clinically indistinguishable from other viral respiratory illnesses, like rhinorrhoea, sneezing, and sore throat (8).The

clinical spectrum of COVID-19 varies widely, ranging from an asymptomatic infection to severe and critical pneumonia with high fatality rates.

Among the deceased patients, the commonest observed complications were: acute respiratory distress syndrome (100%), type I respiratory failure (51%), sepsis (100%), acute cardiac injury (77%), heart failure (49%), shock (41%), alkalosis (40%), hyperkalaemia (37%), acute kidney failure (25%), and hypoxic encephalopathy (20%) (9).

The main risk factors reported in the current literature are: age, presence of comorbidities (such as cardiovascular disease, lung disease, diabetes and cancer), high blood pressure and obesity (1,8-12). However, relatively few patients were included in these recent studies, which makes particularly difficult to distinguish a clear link between comorbidity and disease severity.

There are no therapeutics and vaccines available and there is presumably no pre-existing immunity in the population. The only option available is using broad-spectrum antiviral drugs like Nucleoside analogues and also HIV-protease inhibitors that could attenuate virus infection until the specific antiviral becomes available.

Recently, Gautret et al.(13) treated 3 categories of COVID-19 positive patients (6 patients were asymptomatic, 22 had upper respiratory tract infection symptoms and 8 had lower respiratory tract infection symptoms) with hydroxychloroquine (600 mg, daily). Depending on their clinical presentation, azithromycin was added to the treatment. Hydroxychloroquine treatment was significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect was reinforced by azithromycin (13).

Extensive measures to reduce person-to-person transmission of COVID-19 are required to control the current outbreak. Special attention and efforts to protect or reduce transmission should be applied in susceptible populations including children, patients with chronic disease, health care providers, and elderly people. Prevention measures, such us shutting down public transportation and change in the personal behaviours (wearing masks and reducing contact with others), are strictly recommended.

In the United Kingdom, the National Health Service (NHS) has written to ~1.3 million people considered to be at highest clinical risk from COVID-19 to inform them that they should stay at home at all times and avoid all face-to-face contact for a period of at least 12 weeks. People falling into this highest clinical risk group include:

1. Solid organ transplant recipients;
2. People with specific cancers;
3. People with severe respiratory conditions including all cystic fibrosis, severe asthma and severe chronic obstructive pulmonary disease (COPD);
4. People with rare diseases and inborn errors of metabolism that significantly increase the risk of infections [such as severe combined immunodeficiency (SCID), homozygous sickle cell];
5. People on immunosuppression therapies sufficient to significantly increase risk of infection; and
6. Women who are pregnant with significant heart disease, congenital or acquired.

People are considered in a wider vulnerable group in presence of chronic heart or respiratory diseases, chronic kidney, or liver disease, such as hepatitis and in presence of splenectomy (https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites; Updated: 11 April 2020).

Thalassemia and risk factors

β-thalassemia are a heterogenous group of hereditary anemias caused by gene mutations affecting the production of α- or β-globin (14). Three main forms have been described: transfusion-dependent β-thalassemia (TDT; thalassemia major), nontransfusion-dependent β-thalassemia (NTDT; thalassemia intermedia) and thalassemia minor. Individuals with TDT usually present within the first two years of life with severe anemia, requiring regular red blood cell (RBC) transfusions. Regular transfusion therapy leads to iron overload-related complications including heart, liver, and endocrine glands (14).

Over the last few decades, there has been a considerable advance in optimizing patients' management with RBC and iron chelation therapy. Nevertheless, overt hepatic disease (such as: fibrosis, cirrhosis and hepatocarcinoma) (15,16), heart failure and arrythmias (17) can be detected in early adulthood. In suboptimal treated patients, an early onset of endocrine

disorders in childhood, adolescence, or early adulthood (e.g., hypogonadism, hypothyroidism, biochemical hypocortisolism, hypoparathyroidism and diabetes) have been also reported (18,19).

COVID-19 is such a new disease and much still needs to be learned about it. The number of infected patients with thalassemia is not fully known, although a small cohort of Italian patients, in Northern Italy, 10 with TDT and 1 with NTDT experienced a COVID-19 disease (20).

Their mean age was 44±11 years (range 31-61 years) and 55% (6/11) were females. One patient had pulmonary hypertension treated with sildenafil and 8 were splenectomized. 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 patient, with a history of diffuse large B-cell lymphoma treated with chemotherapy in the previous year but currently in complete remission, was admitted for high fever and bone marrow hypoplasia, lymphopenia, and agranulocytosis while was on treatment with deferiprone. 6/11 were hospitalized, but no one required mechanical ventilation. The clinical course ranged from 10 to 29 days (20).

This contribution is intended to review the current literature on the potential risk factors in patients with thalassemias.

Risk factors

Blood transfusion

Although coronaviruses usually infect the respiratory tract, viral shedding in plasma or serum may happen and so a theoretical risk of transmission of coronaviruses through the transfusion of blood products should be considered (21,22).

Currently there is no evidence that the coronavirus may be transmitted through donated blood and it is advisable to maintain the individual's chronic transfusion regimen (22,23). However, careful monitoring is mandatory since many unknown's knowledge are still present and further studies should continue. Therefore, while offering some reassurance, it does not negate the need for caution with the new coronavirus.

Iron overload and oxidative stress

Iron overload is the main cause of oxidative stress in β-thalassemias by the increased production of reactive oxygen species (ROS) and free radicals (24,25). It has been thought that oxidative stress causes elevation of immune system senescent cells ("premature immunosenescence") (26). Antioxidant therapy can be effective for the immune system function in oxidative stress conditions.

Selenium is an essential element for biosynthesis of glutathione (GSH) contents. Vitamin E acts as an antioxidant on biomembranes and prevents lipid peroxidation more effectively than selenium. Vitamin E is the principal lipid soluble, chain breaking antioxidant in mitochondria, microsomes, and lipoproteins, and can reduce ROS in lymphocytes of β-thalassemia patients (27). Vitamin C is a water-soluble vitamin which neutralizes water soluble radicals and protects cell components from free radical damage and reduces lipid peroxidation derivatives (28).

Citrus fruits which contain hesperidin, an inhibitor of virus divisions, dark grapes, berries and cinnamon which are rich in procyanidins and lectins and seem to block the attachment of the virus to the lungs through the enzyme ACE-2, vegetables, dairy products (rich in vitamin D), seeds and nuts, as a natural source of zinc, that can help the immune system. Green tea and chamomile, which contain the natural antioxidant, and lastly, probiotics are recommended and beneficial in thalassemia patients against viral infections (29).

Iron chelation and splenectomy

There is no evidence indicating relation between iron chelation and susceptibility to SARS-Cov-2 infection or COVID-19 severity. Therefore, if a patient is asymptomatic there is no reason to halt iron chelation. On the other hand, thalassemia patients who became positive for COVID-19 and develop symptoms should discontinue their iron chelation therapy (23).

Splenectomy is a common therapeutic intervention in β- thalassemia. Besides predisposing to infections by encapsulated bacteria, splenectomy has also been correlated with quantitative lymphocyte changes and aggravation of the immunological effects of multiple transfusions, due to the reduced clearance of immune cells (30).

At present, there is no evidence to prove that splenectomy is associated with an elevated risk of SARS-CoV-2 viral infection, compared to general population (23).However, patients whose spleen has been removed must be evaluated for concomitant bacterial infection, which may happen along with COVID-19 and start antibiotics if needed (23).

Chronic liver disease

Possibly, patients with advanced chronic liver disease are at increased risk of infection due to cirrhosis-associated immune dysfunction (20). The same could be true for patients after liver transplantation. However, currently, there are only limited data available and there are still many open questions (31,32).

Cardiac complications

Although in COVID-19 the clinical manifestations are mainly respiratory, with the growing number of infected patients, major cardiac complications have been reported in a considerable number of patients (33,34).

SARS-CoV 2 infection is associated with a variety of proinflammatory mediators that may play important roles in the pathophysiology of cardiac and arrhythmic complications. In a single center study, cardiac injury was observed in 19% of hospitalized patients with COVID- 19, and it was associated with higher risk of inhospital mortality (33,34).

Therefore, a close cardiovascular surveillance is advisable, particularly in thalassemic patients with increased baseline risk due to previous cardiac comorbidities, such as: thalassemic patients with a cardiac T2* <10 ms, or with a personal history of previous or current impairment left ventricular function, or severe iron overload, or with a liver iron concentration (LIC) >14 mg/g/dry weight, or with a serum ferritin level >2,000 ng/ml (35-38).

Diabetes and adrenal insufficiency

Chronic hyperglycemia negatively affects immune function and increases the risk of morbidity and mortality due to any infection and is associated to organic complications. (39).

Diabetes patients have impaired immune-response to infection both in relation to cytokine profile and to changes in immune-responses including T-cell and macrophage activation . Poor glycaemic control impairs several aspects of the immune response to viral infection and also to the potential bacterial secondary infection in the lungs (39-41).

Therefore, it is recommended that patients with diabetes maintain a good glycemic control, because it might help reduce the risk of infection itself and may also modulate the severity of the clinical expression of the disease (39). Moreover, it is advised to ensure adequate stock of medications and supplies for monitoring blood glucose during the period of home confinement. Social distancing as well as home confinement must be adopted and crowds hospital waiting rooms should be avoided.

Although endocrine abnormalities are a well-recognized problem in iron-overloaded patients, adrenal insufficiency (AI) and its consequences are underappreciated by the hematology community (42). Several studies have reported a significant prevalence of "biochemical" AI, ranging from 18% to 45% in patients with thalassemia (43), with an increased prevalence in males over females (92% vs. 29%, P=0.049) (44).

Based on current data, there is no evidence that patients with adrenal insufficiency are at increased risk of contracting COVID-19 (39). However, the high prevalence of biochemical AI (42,43), due to iron overload, may decrease the patients' ability to fight against infections, including COVID-19, so that the possibility of low-dose glycocorticoid supplementation should take into consideration.

Immune response

Genetic differences are well-known to contribute to individual variations in the immune response to pathogens. However, when a protective immune response is impaired, virus will propagate and

massive destruction of the affected tissues will occur, especially in organs that have high ACE2 expression, such as intestine and kidney. The damaged cells induce innate inflammation in the lungs that is largely mediated by proinflammatory macrophages and granulocytes (45).

Infectious complications and immune abnormalities have been considered as causes of morbidity and mortality in β-thalassemia. A wide spectrum of immune abnormalities has been described in

β-thalassemia patients receiving multiple transfusions (46). These abnormalities are both quantitative and functional and concern several components of the immune response (46-50).

Iron overload has been implicated as the main precipitating factor of immune deficiency in β-thalassemia (47,48). Iron directs the immune response toward a T helper (Th)-2 response pattern, which is unfavourable for fighting a bacterial or viral infection. Cellular iron availability modulates the differentiation and proliferation of Th1 and Th2 cell subsets, which may partly be related to the different dependence of cells on transferrin-mediated iron uptake (47).

Conclusions

Hemoglobin disorders including thalassemias are generally not associated with respiratory diseases but anemia and iron-overload involving the heart, lungs (pulmonary hypertension), liver disease, diabetes and even the immune system, can encounter these patients to have higher risk of complications from SARS-COV-2 infection than normal population, specially when they become older. The few reported cases of SARS-CoV-2 infection in people with thalassemias might reflect the efforts to minimise social contacts or other unclarified reasons, such as lower beta globin protein as a possible target of COVID-19 in these patients (51). This effort might be considered a success, but there is no room for complacency and the directive for social shielding of both the patient and family members remains clear and important.

More data should be collected to better characterise the impact of SARS-CoV-2 infection in patients with thalassemias. Therefore, a multicenter registry and the collection of comprehensive data from both positive COVID-19 thalassemia major and non-transfusion dependent thalassemia are necessary to clarify debated issues.

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