COVID-19 and Thalassaemia in Iran

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Abstract

Coronavirus disease 2019 (COVID-19) has had and continues to have a significant medical, public health, social and economic impact on every society around the world. Some groups of chronic patients including thalassaemia and other haemoglobin disorders were considered from the beginning of the pandemic, as vulnerable and high risk ones with regards to a more severe clinical outcome of the infection with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). This is because patients with thalassaemia can present with many and multiple co-morbidities including diabetes, heart, liver, endocrine and other conditions mainly secondary to iron overload and consequent to ineffective or suboptimal medical care and/or adherence to chelation treatment in particular. Transfusion dependent patients with β-thalassaemia have been greatly affected across the world, including in Iran, a country geographically situated in the so called *thalassaemia belt*. Iran with about 20,000 patients with β-thalassaemia and quite successful disease specific prevention and management national programmes faced challenges similar to others. Blood shortages for example consequent to COVID-19 precaution measures taken in every country to contain the virus and the difficulties in accessing drugs including lifesaving ones (iron chelation medication) constitute major challenges. In Iran however, and despite the multiple difficulties as described above, SARS-CoV-2 had a rather small impact regarding infection rates as compared to the rest of the countries, albeit a higher mortality rate reaching 26.5% amongst COVID-19 diagnosed patients.

More comprehensive data however from a bigger number of patients with thalassaemia across the world infected with SARS-CoV-2 is necessary to draw any reliable conclusions as to the level of vulnerability to SARS-CoV-2 and importantly the clinical impact of this virus in these patients.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected millions across the world, with an ever increasing infectivity and mortality rate, currently translated to 5,657,529 confirmed cases of COVID-19 and 56,254 deaths as per the WHO's official report (last update 29 May 20).[1] The SARS-CoV-2 causes a highly variable disease spectrum in the upper respiratory tract that ranges from nasopharyngeal symptoms to full blown pneumonia[2,3] while currently the virus has been demonstrated to have multi-organ impact. Despite an apparent disassociation between this viral infection and inherited haemoglobin disorders, there are particular challenges and risks to patients affected by thalassaemia and sickle-cell disease, due to the specificities of their pathophysiology and lifelong treatment needs.[4]

Thalassaemia and sickle cell disease (SCD) are the most common monogenic disorders in human with about 7% of the global population carrying an abnormal haemoglobin gene.[5] These disorders are characterised by multi-systemic involvement and need for intensive lifelong therapy and multidisciplinary care.[6,7] If left ineffectively controlled and managed, they lead to a number of severe complications and a very poor quality of life of patients. They are associated with high rates of morbidity and mortality and significant medical, public health, social and economic repercussions. As a consequence, if left untreated or sub-optimally treated, they contribute significantly to the national/regional and global disease burden.[8]

On the other hand, and consequent to the dramatic progress achieved in the last 2-3 decades in the area of the control of these disorders, one may today safely state that they can be effectively prevented and well managed when primary and secondary prevention and management programmes are developed and included in the context of diseases' specific national strategies.

Survival rates, age distribution and reduction of morbidity and mortality rates constitute important indicators of the success and effectiveness of such programmes. These are seen and adopted particularly in the Western world and in some very few countries beyond, including the Islamic Republic of Iran, where however less than 10% of the global patient population is born and live. In these countries, patients with haemoglobin disorders, particularly those born after the 1980s, have been growing normally, have achieved a very satisfactory quality of life and almost full social integration.[5] In these settings, patients are now facing a new spectrum of co-morbidities related to ageing.[9]

The challenges however are multiple and magnified for patients living in the developing world due but not confined, to different priorities in the area of public health, including communicable diseases, different priorities on non-communicable diseases but also to poor resources and weak health infrastructures. These, in conjunction with the absence of universal-coverage health care systems result in the provision of suboptimal medical and other care to patients particularly those with chronic disorders including patients with haemoglobin disorders. Under such conditions, the risk of these patients developing serious multiple medical complications, including cardiac, hepatic, endocrine disease and other, is very high. Inevitably, one may anticipate that these patients are at significantly higher risk for a more severe infection with the SARS-CoV-2.[10]

In this widely heterogeneous state of affairs across the globe which reflects the widely different quality in the standards of medical and other care provided to patients with haemoglobin disorders within and across countries, within and across the different regions of the word, the COVID-19 pandemic made in the early 2020 its unexpected grand entry.

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Iran Health Authorities, more specifically Ministry of Health, Treatment and Medical Education has announced since early March (March 6, 2020) that all patients with chronic diseases constituted vulnerable groups of citizens with regards to the level of risk for infection with SARS-CoV-2 and a more severe clinical progression of its infection.[11]

The World Health Organization (WHO), the Centers for Disease Control and Prevention (USA) and other official health bodies/Associations at national, regional and international level have recommended to the world, from the early days of the declaration of the pandemic COVID-19, the specific precautionary measures that had to be taken at country level for the containment of the infection in the community but also amongst the vulnerable groups.

In addition, and in relation to haemoglobin disorders, Thalassaemia International Federation (TIF) responded promptly to COVID-19 pandemic through the publication and worldwide distribution of informational material (https://thalassaemia.org.cy/) amongst others, on ways: to i) secure the safety of access of patients with thalassaemia and Sickle Cell Disease (SCD) to their treatment centres; ii) to empower blood donors to continue donating aiming to keep as far as possible a safe level of red blood cells (RBCs) at national level for the transfusion needs of these patients; iii) to support health authorities and treating physicians to better understand the levels of risk amongst patients with haemoglobin disorders; and iv) to update on a continuous basis its data and information with regards to the global research activity with regards to the development of vaccines, therapeutic drugs (including their repurposing) and diagnostic RNA and antibody based testing.[12]

United Nations (UN) in particular underscored the huge social and economic repercussions of the pandemic in addition to medical and public health ones.[13-17] Iran with a population of 8 million, is geographically situated in the so called *world thalassaemia belt* with an estimated 4% of its population being carriers of β-thalassaemia.[18] The control of this disorder, encompassing prevention and management programmes, has been for many years now in the focus of the work and priorities of the Iranian Governments and Health Authorities. The national thalassaemia prevention programme was implemented in 1995 with the simultaneous and gradual development of a wide countrywide treatment network involving 64 medical universities and faculties and 198 to date medical treating centres across the country to provide services for prevention, medical and other care to nearly 19,000 to date registered patients with thalassaemia. Of considerable contribution to the national commendable efforts has been the work of the Iranian Thalassaemia Society and the Charity Foundation for Special Diseases established in 1989 and 1995 respectively. Both of these NGOs focused, and still focus, particular attention and work on supporting the Governments' efforts in strengthening the effectiveness of its national programmes (prevention and management) of thalassaemia and on supporting the many and multiple needs of the patients themselves and their families. The effectiveness of the prevention strategy in particular has been published widely and is well demonstrated by the calculated 90.13% reduction in annual affected births since 2015 and the establishment,[18] in addition to the medical university centres, of another 198 medical centers providing quality medical care based on international standards to all patients across the country. Out of a total of 19,000 patients, 17,342 patients are transfusion dependent and non-transfusion dependent β-thalassaemia patients, consuming in total about 20% of the annual Iranian blood supplies. Considerable focus throughout the years has been placed on the adequacy and safety of blood provided to the patients through its well-structured, quality services of the Iranian Blood Transfusion Organisation (IBTO) which serves as a WHO-EMRO Collaborating Centre since 2013.[14] The achievements of the country are highly commendable both in the area of prevention, acknowledging the many potential challenges anticipated in an Islamic community, as well as in the area of treatment. The production of generic drugs (iron chelation mainly) by Avicenna Pharmaceutical - including Osveral, Desfonak, Nanojade and Deferiprone - aiming to increase accessibility of all patients to lifesaving drugs, has been of pivotal importance.

The study

This report is based on the patients' perspective expressed through their answers in a questionnaire (Appendix I) regarding the impact of COVID-19 on their medical and social care. The questionnaire was developed by patients - members of the Iranian Expert Patients Panel with the support of treating medical experts and was uploaded on the Questant system (https://questant.jp). The link was shared with patients across Iran through the 198 treating centres across the county via different means including Telegram, What's App, and Instagram aiming to compile information and *capture* the response mainly of patients over 16 years of age.

In addition to the patients' perspective *captured* through their responses to the questionnaire, medical data was provided by the medical officer in charge of the medical Universities related to the patients COVID-19 confirmed, who died (Table 1).

Possible study limitations

1. Questant website is a Japanese website. Based on the feedback of some patients it was impossible to reach out to it without VPN. The investigations showed that some ADSL offering companies had blocked access to this site and the patients/subscribers of these companies had to provide responses to the questionnaire by the use of VPN.

Table 1. COVID-19 in patients with thalassemia who died.

No	Gender	Age	Thalassemia type	The last measured ferritin level	Diabetes	Heart problems	Pulmonary problems	Liver failure	Splenectomy	HCV or HIV affected record
1	Male	25	Intermedia	1980	No	No	No	No	Done	No
2	Female	35	Intermedia	600	No	No	No	No	Done	No
3	Female	32	Major	2700	No	No	No	Yes	Done	No
4	Male	30	major	1000	Yes	Yes	No	Yes	No	Indefinite

2. Given the limited membership of thalassaemia parents in virtual channels and networks for information dissemination, the under 16 year old patients were excluded from entering the website and providing information.
3. Given the fact that patients were discharged based on clinical symptoms and not on definite laboratory test results[15] and further given the fact that no diagnostic tests for non-hospitalized, symptomatic patients was conducted in Iran,[16] only the mortality rate of patients in hospitals constitutes to date a is reliable marker of how the virus has impacted on patients with thalassaemia. Therefore, it is not possible to deliver a definite opinion on the rate of the affected and the recovery rate of COVID-19 patients.[17]

Results

- 469 patients with thalassaemia across 198 medical centres answered the questionnaire, out of whom only 100, 21.3%, (39% male and 61% female) provided valid responses;
- 55% of those who responded had an average age between 30-39 years of age, except in the base of Sistan va Baluchestan province where the patient population is in majority young patients below 16 years of age. The participation was thus only 6%.
- The research participation rate in the capital Tehran has been 19% and that of the thalassaemia prone province of Mazandaran[18] 14%. Out of the total 32 provinces in the country divisions, 18 provinces actively participated in the study.

Responses obtained

In relation to blood shortages, impressively 70% of the patients responded that COVID-19 had no adverse impact neither on the frequency of their transfusion nor on the number of monthly units of RBCs they received. 14% reported a decrease of the frequency and/or number of units and not an insignificant percentage however of 10% reported a negative impact on their transfusion therapy. This latter however was on account of their own accord refusing to access the transfusion/treatment centres expressing fear of their safety in relation to COVID-19. Indeed 57% of the participants reported that they perceived absence of protection equipment, for their safe movements and traveling to transfusion centres and relatively very confined measures taken in ensuring safe accessibility of patients to their treatment/transfusion centres. 76% reported reduction to no access at all to iron chelation drugs. Major cause of drug unavailability was reported to be the difficulties in importing medicine into Iran, coupled with the reduction in the production of locally produced generic forms of the drugs. Additionally, patients reported shortage of blood transfusion related equipment including leukocyte filters (4%), Deferoxamine delivery related equipment (Syring, scalp vein, and pump) (7%) and medicines related to common medical conditions affecting the whole society of Iran including patients with thalassaemia. More specifically in the latter context, the patients reported shortages of medicines for heart (14%), diabetes (4%), thyroid (7%), and osteoporosis (6%), common secondly medical complications mainly related to iron over load.

COVID-19 pandemic had significant to severe social and economic repercussions in every society of every country in the world including Iran and particularly affected severely those counties devoid of universal health coverage based systems.

In Iran however, with universally covered health care system and with significant sensitivity and focus on thalassaemia on behalf of the Governments for decades now, a significant portion, 68%, reported no complaint of being affected: 25% reported being satisfied and 43% as being satisfied with very minor challenges in their financial state. About a third (32%) however reported being seriously affected with no governmental or charity support. 48% of those who reported worsening of their financial status, mentioned that this was consequent to losing their jobs. 29% of patients complained on negative environment in their working places (particularly with regards to safety precaution measures taken). During the crisis 15% reported that they felt that their physical fit was affected while 10% complained on issues of adverse effects on family relations. Importantly, nearly half, 42%, reported negative impact on their mental health in relation mainly to the quarantine applied during COVID-19 pandemic.

SARS-CoV-2 infected patients with thalassaemia in Iran

Fifteen[15] patients with thalassaemia were reported to be affected by COVID-19, out of which 11 recovered while 4 died. Table 1 below describes the medical characteristics only of the 4 patients who died.

Discussion and Conclusions

The above findings in Iran, even though preliminary and lacking more comprehensive, mainly medical, information, demonstrate that in countries with strong health and blood transfusion infrastructures, universal health and social coverage and national focus on haemoglobin disorders through disease specific prevention and management strategies such as those found in Iran, had to date the minimum possible negative impact of COVID-19 on patients with haemoglobin disorders mainly thalassaemia. As this study confirms, In Iran, there has been ongoing, almost with no interruption, blood transfusion therapy during the pandemic of these patients which has allowed no or minor regression of their health status and in particular with regards the pre transfusion haemoglobin levels which were kept at acceptable levels of 9-10 g/dL. Iranian extensive blood donors network and quality blood transfusion services managed to keep safe levels of red blood cell reserves for the majority of the patients with thalassaemia at all times during the *lock down* period of the pandemic. Blood shortage has been a challenge that was not possible to be sufficiently addressed in the greatest majority of countries particularly of the developing world during the pandemic and to date.

In addition, the existing robust patient blood management programmes and high level adherence to national precaution measures taken in Iran with regards to cancellation/postponement of elective surgeries have in addition contributed significantly to counter balance to a great extend any blood deficiencies that may have been observed.

However, major challenges in Iran, perhaps more related to the political environment in addition to the lockdown condition mandated by each Government all over the world, included shortage of life-saving drugs, mainly those either imported or locally manufactured. For similar reasons, the shortage of protective equipment and the absence of the early, prompt measures for securing safe access of patient to their treating centres such as those recommended by TIF,[12] presented important challenges in mainly keeping uninterrupted the medical care of these patients. The social and economic impact of course of COVID-19 was quite heterogeneous across the world with its extend very much dependent on the HDI of the country, its social care system and its health care system whether coverage being universal or out of pocket. In Iran responses demonstrated a quite mild to moderate diversion from pre COVID-19 social and economic standards. Certainly unprepared-

ness and unprecedented negative consequences in the areas of health care systems and public health have been major observations in almost every country of the world including Iran. In fact, this pandemic demonstrated the need for more global solidarity and investments in these areas.

The infection rate amongst the patients with thalassaemia in Iran based on publicly reported data until 8th of May 2020, was 0.078%, considerably lower than in the general population which was 0.12%]. On the other hand, however, the mortality rate in the infected patients was 26.7% versus 6.313% in the general population, a much higher than that noted in Italy and the UK in their published reports.[19-21] This may demonstrate the increased risk and vulnerability of patients with this disorder albeit more comprehensive information on a bigger number of infected patients is needed to confirm any conclusions. The to date's small numbers worldwide, reported in published literature and to TIF, may be related to underreporting, misreporting, no reporting, misdiagnosis or no diagnosis.

Today however and despite the odds, the world is equipped with extremely advanced scientific weapons, tools and technologies than even before, making us all very optimistic with regards to the prompt development of one or more effective and safe vaccine(s) and therapeutic drugs to fight the SARS-CoV-2 infection. Certainly more comprehensive reporting is needed for patients with thalassaemia and generally haemoglobin disorders across the world and in Iran. This is essential to gain more knowledge and experiences on the clinical impact of this infection in these patients with an underlying hereditary disease characterized by an immense genetic variability and very frequently associated with many and multiple co-morbidities, the level of which depends mainly on the quality of medical and other care they receive.

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