Hemoglobin disorders in Europe: a systematic effort of identifying and addressing unmet needs and challenges by the Thalassemia International Federation

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Abstract

Hemoglobin disorders (thalassemia and sickle cell disease) are a group of hereditary anemias that today occur across the world. The recent population movement has led to a steady increase of carriers and patients in all countries of the European Union. Requiring complex monitoring and treatment and, as a consequence, well-organized and nationally coordinated, supported and funded services, these lifelong conditions are now *visible* to healthcare services in the EU. The purpose of this study is to provide an overview of the current situation pertaining to these disorders, as perceived by the patient/parent community that the Thalassemia International Federation (TIF) represents. The aim is to establish a comprehensive understanding of the situation and unmet needs faced by migrants with thalassemia. The implementation of activities by TIF in 2018-2020 to identify and address these challenges, paves the way to increased awareness, education and policy changes building on international expertise and knowledge that will enable the provision of state-of-art clinical management services thus guaranteeing an improved quality of life. A bird's eye view of the prevalence of these disorders is presented contributing to the further understanding of challenges met by both patients and healthcare professionals in the receipt and provision of quality healthcare respectively.

Introduction

Hemoglobin disorders are a group of hereditary anemias caused by genetic mutations affecting the production of the globin chains of the hemoglobin molecule. Their prevalence seems to be related to past or present prevalence of *Plasmodium falciparum* malaria across the globe, since it appears that healthy carriers have a selective advantage over non-carriers as far as survival to malarial infection is concerned. There is a geographical coincidence of haemoglobinopathy prevalence, with those parts of Europe where malaria was rampant in the past.[1] Cyprus is a primary example of this phenomenon, since until its eradication in 1948, malaria was a major public health problem; the beta thalassemia carrier rate was recorded to be 15-18%.[2] Lowland regions of Greece, Italy and Turkey were similarly affected.

Geographical distribution in Europe

High prevalence globally, for both thalassemia and sickle cell disease (SCD), appears to range from the Mediterranean basin across Africa and the Middle East to the Far East reaching the Pacific coast. In the European setting, the countries in which the indigenous population is most affected are the South of France, Italy, Greece, Albania, Turkey and the Mediterranean islands. Some countries to the north of these, such as the Balkans are less affected as is the Iberian Peninsula. Southern Russia and the Caucasus have a variable prevalence, with the exception of Azerbaijan which has a high prevalence. North of these areas are most European countries where beta and alpha thalassemia are extremely uncommon (with around 0.1-0.2% of the population being heterozygotes), while sickle cell genes and other variants are almost unknown in the indigenous populations (Figure 1).

Historical population movements in the early and mid-20th century from high prevalence countries have introduced these disorders to the countries of Western Europe (*e.g.* UK and France) and the Americas (*e.g.* USA, Canada and Brazil). Furthermore, more recent population movements to Europe, of different causality, voluntary or forced, have changed the European landscape in the area of hemoglobin disorders, and have led to a steady increase of carriers and patients in all countries of the European Union, including formerly low prevalence countries such as Scandinavian countries (*viz*. Denmark, Sweden) and Central European countries (v. Slovakia, Czech Republic).[3,4] A migration flow from the east has followed a transit route through Turkey, Greece and the Balkans aiming to reach the countries of Western and Northern Europe (mainly France, Germany and Sweden). From Africa, the origin of most sickle cell carriers, increasing numbers are entering the European continent mainly across the Mediterranean to Italy and Spain. Some among of the persons originating from high prevalence countries of the Middle East, South East Asia and sub-Saharan Africa are likely to be healthy carriers of these disorders or indeed patients. Likewise, persons from Afghanistan, Iraq, Syria, Thailand and Turkey, entering Europe from the Eastern borders of Greece and the Balkans might be carriers of thalassemia or HbE genes. In Germany, only about 1000-1500 sickle cell patients were recorded in 2014, while in 2016 a neonatal screening study revealed that 1 in 2385 newborns are SCD carriers, probably of Sub-Saharan ancestry.[5,6] The documented number of people settling in Europe until 2015 from high prevalence areas and the subsequent estimated number of carriers based on prevalence rates in their countries of origin is demonstrated in Table 1.[8-14] In the absence of an internationally accepted definition of *migrant*, in this publication the term will be used to define any individual who lives outside their country

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Novelty statement: An updated bird's eye view of the prevalence of hemoglobin disorders is presented following the recent migration flow to Europe in 2015. Understanding the distribution of carriers and patients across Europe, contributes to the further understanding of challenges met by both patients and healthcare professionals in the receipt and provision of quality healthcare respectively.
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of origin for whatever reason either voluntary or forced (*e.g.* conflict, poverty, political unrest, natural disasters, *etc.*).[5,6]

Medical progress now allows for the survival of haemoglobinopathy patients who would have passed away in early childhood until a few decades ago. The increasing numbers of patients together with intensified population migrations from high prevalence countries today make hemoglobin disorders 'visible' to the health services of countries which previously regarded them as extremely rare, having brought new challenges to European health services.[5] Persons born outside Europe are generally increasing in Europe, but in the context of hemoglobin disorders, it is those migrants that have arrived more recently (after 2012) from high prevalence countries, that are the focus of this study.

Figure 2 represents the number of migrants from high prevalence countries up to 2015. These estimates concern relatively recent migrations, while other second and third generation migrants are not counted. Since then and up to the end of 2019, another 855,000 have arrived, mainly from high prevalence locations (IOM data).[7] In addition, unregistered/undocumented illegal entries are estimated to be high, especially from sub-Saharan Africa where the HbS gene is present in high prevalence. Frontex, the European Union frontier police[15] estimate that from 2009 to mid-2020, 317,000 such migrants were detected from Sub-Saharan African countries and another 102,000 from the Maghreb countries and Libya. It is possible that many others may not have been detected. Therefore, it is speculated that as many as half a million people from high prevalence of sickle cell carriers may have entered Europe, with Spain, Italy, France, Germany and the UK being the main recipients. This means that there are around 20 million settlers in European countries of low prevalence for hemoglobin disorders who may have abnormal hemoglobin genes (with the exception of Italy which has both indigenous and migrant high risk populations). This is around 5% of the total population of the most affected countries.

The increasing size of this public health problem with considerable socio-economic repercussions in Europe is demonstrated by these estimations. Registries, health records and other databases are essential tools for gathering information, which help to define the epidemiology, clinical outcomes and the natural history of these rare conditions, which have been on the rise in much of Northern and Western Europe for quite some time now but the migration crises playing out since 2015 has made these disorders more visible as numbers keep rising. Information from such healthcare tools will help to improve the much needed quality of multidisciplinary care and to plan services, as well as to assist in research initiatives including clinical trials. Thus, the development of an EU-wide comprehensive disease-specific Registry is pivotal for monitoring not only the spread of hemoglobin disorders in each country but as a health planning tool that informs national policy for the development of targeted specialized care services and allocation of appropriate financial and human resources (*Farmakis D, Angastiniotis M, Eleftheriou A. Thalassemia registries - A call for action: A report of the Thalassemia International Federation; 2020 - undergoing peer review*).[16]

Services for hemoglobin disorders

These lifelong conditions require com-

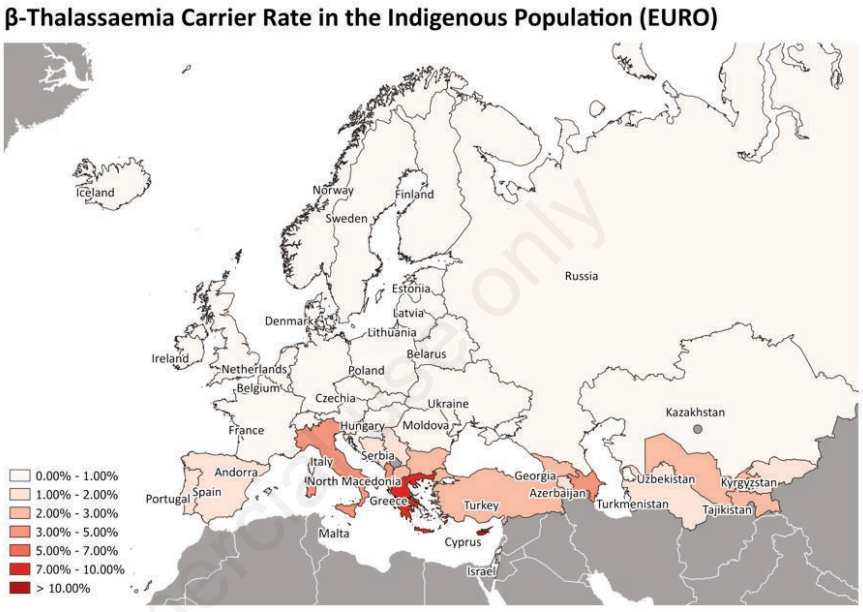

Figure 1. β-thalassemia carrier rates in the indigenous population of the WHO European Region (2020).

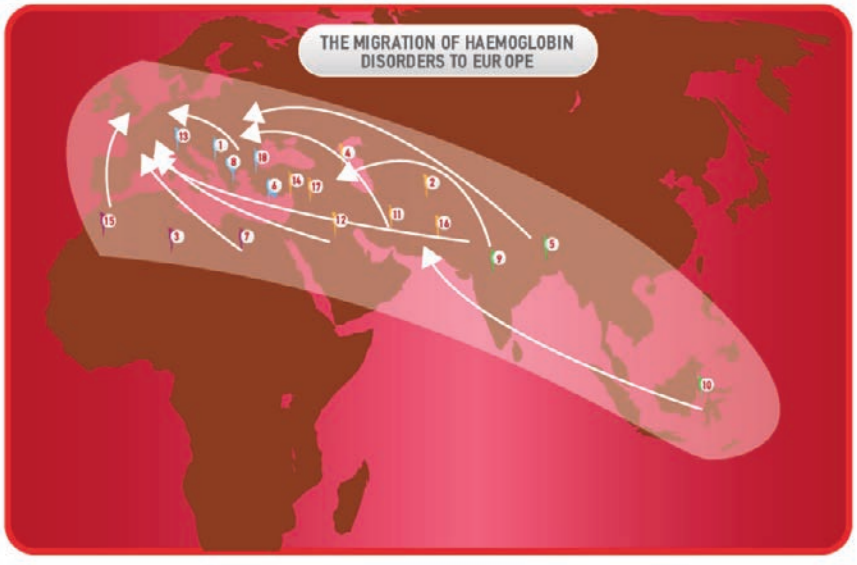

Figure 2. Map showing migration flows into Europe.

plex monitoring and treatment and, as a consequence, well-organized and nationally coordinated, supported and funded services. These services include the need for regular blood transfusions and iron chelation supported by multi-disciplinary medical collaborations in expert centres[17] as described in the International Guidelines for Clinical Management of Thalassaemia.[18] Such organized multidimensional care has been demonstrated to have converted lethal childhood disorders to chronic conditions of adult life,[19] allowing patients to achieve a near normal life. Scattered minority groups in an environment in which these are rare conditions, may not have access to the expert care that they need. Not being optimally treated will result in poor quality of life, more complications and even more expert and expensive clinical management. In the north and western European settings, such services are available in academic and other reference centers. The European Commission, in its rare disease policy and according to the Regulation 2011/24/EU on Cross-Border Healthcare, has promoted in the context of a specific legislation the development of a system of networking (European Reference Networks) so that a patient with a rare condition may be treated in a local health facility, which is networked with a reference center, in a shared care situation.[20] In the case of blood disorders, such as thalassemia and SCD, the Eurobloodnet consortium is the responsible European Reference Network[21] created to put into practice the proposed hub and spoke system of service delivery to rare disease patients.

The various issues faced by migrants are, as yet, only partially met in Europe as is the case with many other rare diseases. There are a variety of factors that influence the access of migrants to optimal care: i) unfamiliarity with the health system and the available services in the host country; ii) language barriers since most migrants do not speak the language and are often of a poor educational background; iii) difficult and delayed diagnosis, both because the laboratories in the vicinity in which the migrants have settled may not be familiar with complexity of diagnosis; iv) they may not have a diagnosis or medical history from their country of origin; v) families are concerned with social issues, such as finding employment and housing as well as facing prejudice and xenophobia, and thus may delay any health concerns.

The purpose of this study is to provide an overview of the current situation in Europe pertaining to thalassemia and SCD, as perceived by the patient/parent community that the Thalassemia International Federation (TIF) represents. This investigation has been undertaken in the context of the '*Thalassemia In Action (THALIA)*'

Table 1. The prevalence of thalassemia and sickle cell disease in European countries affected by the migration crises based on data from the International Organization for Migration site.7

Country	Carrier rate of β-thalassemia and SCD in the *indigenous* population	No. of accepted migrants from high prevalence areas with thalassemia and low prevalence of SCD	No. of accepted migrants from high prevalence SCD areas	*Estimate* of the patient population (indigenous and migrant)
Austria	0.2%	311,000	14,000	60-79 BTS* 132 SCD*
Belgium	0.28%	408,000	64,000	62 BTS* 358 SCD*
Denmark	0.2%	171,000	16,000	83 BTS* 236 SCD*
France	0.8%	3,993,000	511,000	666 BTS[8,9] 22,000 SCD[10]
Germany	0.2%	3,427,000	127,000	600-1600 BTS* 2000 SCD[11]
Netherlands	0.1%	748,000	71,000	350 BTS* 2000 SCD*
Norway	0.1%	162,000	47,000	100 BTS* ? SCD
Portugal	1.44%	16,000	75,000	40 BTS* 800 SCD
*Serbia	1.2%	Transit country - Migrants not settled	Transit country - Migrants not settled	3-5 BTS*
Spain	1.6%	1,032,000	228,000	100 BTS[12,13] 800 SCD
Sweden	0.3%	535,000	84,000	150 BTS* 584 SCD
Switzerland	0.4%	531,000	35,000	62 BTS* 194 SCD
Italy	4.3% β-thalassemia 2.1% SCD	1,621,000	284,000	7044 BTS* 2000 SCD
UK	0.1%	2,652,000	1,005,000	1564 BTS 14,000 SCD[14]
Total	-	15,679,000	2,581,000	-

SCD, sickle cell disease; BTS, β-thalassemia syndromes. *Information on the number of patients, where access to an updated registry is not available are derived from information provided by national experts, either during TIF visits or during the TIF European Symposium for Thalassemia and Sickle Cell Disease (December 2020).

Framework Partnership between the Federation and the European Commission, initiated in 2018, focused on identifying and addressing the unmet needs and challenges of patients living within the EU with a particular emphasis on migrants with thalassemia and SCD in France, Germany and Sweden (as host countries), and Austria and Serbia (as transit countries), known as '*THALIA countries of priority*'.

Methodology

Through the application of a mixed methods approach, information has been obtained by patients/parents and healthcare professionals working in the field of hemoglobin disorders through a variety of vehicles, as described below. The aim being to establish a comprehensive understanding of the situation and unmet needs faced by the thalassemia patient community living in France, Germany and Sweden, Austria and Serbia. Onsite visits were supplemented by a literature search concerning epidemiology and service description.

Onsite delegation visits

In each visit a delegation was composed of medical specialists and/or patient advocates along with a local TIF member.

During each visit, the TIF delegation met with medical specialists, health authorities and patient associations (if in existence) and individual patients/parents to map the situation and tailor the support (*e.g.* education, awareness raising, advocacy, *etc*.) provided by TIF accordingly. The TIF delegation team, in collaboration with the local medical community and patients' association, observed a situation analysis. The COVID-19 pandemic has necessitated in 2020 the transition to virtual delegation visits.

Thalassemia-specific prevalence database and literature findings

TIF maintains a thalassemia-specific prevalence database to monitor the geographical distribution of patients throughout the EU and supports the improvement of existing, and the creation of new public health policies and legislations by national health authorities. This is largely based on published literature but also on locally derived information particularly concerning patient numbers. Although many publications offer a significant contribution towards understanding the epidemiology of these disorders, the lack of reliable and comprehensive national registries for thalassemia and haemoglobinopathies at present suggests a gross underestimation of their prevalence in Europe. In addition, knowledge and understanding of the distribution of patients and prevalence of the disease in each country is a huge contributing factor to public health planning.

Results

A total of 20 onsite TIF delegation visits were conducted to the five THALIA countries of priority (France, Germany, Austria, Sweden and Serbia), between January 2018 - March 2020. In addition, 15 virtual meetings took place during 2020 with patients/parents and treating physicians from each of the aforementioned countries. The total number visits/virtual meetings and persons (patients/parents and medical specialists) which the delegation teams interacted per country with are shown in Table 2.

An overview of the available infrastructure including national policies for screening and access to healthcare services for migrants, diagnostic competencies, treatment centers visited during the THALIA program with expertise in the clinical management of hemoglobin disorders as well as support groups for patients transpired through efforts exerted in the context of this study, as demonstrated in Table 3.

Onsite visits to hospitals, treating centers, laboratories and patient support groups were conducted in each of the delegation visits, in order to engage in discussion with the relevant stakeholders to obtain information about services provided (either at the specific health providing unit or across the country; Table 4) and to map the epidemiological situation in each country (Table 5).

Table 2. TIF Delegation Team interactions with stakeholders in the THALIA countries of priority.

	France	Germany	Austria	Sweden	Serbia	Total
No. of visits/virtual meetings	10	9	10	4	3	36
No. of patients/parents	123	143	140	22	57	485
No. of medical specialists	158	66	45	16	12	297

Table 3. Available infrastructure for patients in THALIA countries of priority.

Infrastructure		Austria	France	Germany	Sweden	Serbia
National Screening Policy		No	No	No	No	No
Diagnostic Laboratories		Yes	Yes	Yes	Yes	Yes
Treatment Centres Visited		2	2	8	2	1
Patient Support Group (Disease-specific)		No (Created in 2019 by TIF initiative)	Yes (National and Local coverage)	Yes (Several with local coverage)	No	None
Access to healthcare services	Insurance coverage for registered migrants	Yes fully	Yes fully	Yes but several providers with variable coverage	Yes fully	Yes fully
	Insurance coverage undocumented migrants	Covered by NGOs	Scheme exists under State Med Aid	Only for emergency care	Children fully covered; adults subsidized	Transient migrants are supported

Other findings and observations

The dispersal of patients with hemoglobin disorders across the entire host country, as well as the historical settlement of migrants from high prevalence areas, has necessitated the development of centers of expertise in the management of thalassemia and SCD. These centers, are mostly found in urban areas of France and Germany. However, networking with treating physicians and centers in more rural areas appears to be limited. By contrast, in Sweden and Austria services are located in capital cities where hematology departments (pediatric and adult) are providing care for these rare blood disorders but with limited networking. Quality of care was variable in main cities, whilst in rural areas or peripheral towns knowledge on the appropriate clinical management of these disorders is severely limited due to rarity of cases. Patients in Serbia are distinctly even more scarce in comparison to France, Germany, Austria and Sweden, for two reasons: i) migrant patients are sporadic and remain on Serbian soil for a very limited amount of time, transiting to settle in other European countries; and ii) the patients from the indigenous population are very few due to the low prevalence rate.

One striking feature, common to all treating centers visited, is that because of the low numbers of patients, the vast majority of patients transfused in the same center do not know each other and never meet (even though they may be in the next room). This is in stark contrast to the sense of community and belonging experienced by patients in countries where there are significant number of patients, even in Europe (*e.g.* Cyprus, Italy, Greece, UK). Therefore, patients with thalassemia have reported through interviews feelings of isolation and social marginalization, sometimes to a larger extent than patients with SCD who seem to be generally more abundant. This is further evidenced by the absence of thalassemia-specific patient support groups (Table 3) in Sweden, Austria and Serbia; as well as the existence of small number of such groups in Germany and France. Indeed, in the case of the France and Sweden, thalassemia patients appeared to be supported in a limited fashion by the SCD federation and blood cancer association respectively. The efforts exerted in the context of this study since 2018 has seen a shift towards the defining of functional support groups in Germany and Austria and the further empowerment of the patient community in France and Sweden. Serbia, as a transient country for migrants and with extremely low number of patients with thalassemia, necessitates an ad-hoc support approach for individual patients.

High quality laboratory services enabling the diagnosis of carriers, affected patients, prenatal diagnosis and neonatal screening are available in all the THALIA countries of priority. The rarity of encountering these disorders requires further awareness among laboratory personnel to pursue further investigation of low indices, to differentiate between other causes of anemia (*e.g.* iron deficiency) and between patients and carriers. The provision of reliable results using validated methods is imperative, notwithstanding the responsibility for their interpretation lies with the clinicians. Routine screening or genetic counselling policies were not in effect in any country under study. The familiarity of primary care physicians with suggestive symptoms or suspicion of carrier/patient status based on ethnic origin, and hence recommendations for appropriate referrals, could not be assessed at this stage.

Universal health coverage allows for the access of all thalassemia and SCD patients (including documented migrants) to basic treatment (*i.e.* blood transfusion and iron chelation), as well as access to the complex monitoring required in these

Table 4. Summary of Healthcare Services provided to patients with hemoglobin disorders as deduced from TIF Delegation Visits (2018-2020).

Services	Austria	France	Germany	Sweden	Serbia
National registry	No	Yes (separate for thalassemia and SCD)	Yes (SCD registry is active; thalassemia registry is under development)	No	No
National guidelines for the clinical management	No	Yes	Yes (partial adherence)	Yes (only for thalassemia)	No
Pre-transfusion Hb (for thalassemia patients)	Children 9-10 g/dL Adults 6-8 g/dL	Reference centers: 9-10 g/dL Peripheral centers: <9 g/dL	Reference centers: 9-10 g/dL Peripheral centers: Variable < 9g/dL	Reference centers: 9-10g/dL Peripheral centers: Variable <9 g/dL	9-10g/dL
MRI availability for iron overload monitoring	Until 2019 only for children	Limited to Reference Centres	Yes but not systematic referral in all centers	Limited to Reference Centres	Not available
Multidisciplinary care	For adults: On referral	Limited to Reference Centres	Limited to Reference Centres but not well established	Limited to Reference Centres but not well established	On referral
Networking	Not official	Not official	Exists but variable	Not official	None
Genetic counselling	Not organized	Not organized	Organized processes (Lack of disease-specific knowledge)	Not organized	Not organized

SCD, sickle cell disease; Hb, hemoglobin; MRI, magnetic resonance imaging.

Table 5. Estimated No. of patients in each of the THALIA countries of priority.

	Austria	France	Germany	Sweden	Serbia
Thalassemia	60-79	666	600-1600	150	N/A
SCD	132	22-28,000	2000	584	N/A

SCD, sickle cell disease.

chronic disorders. Affordability is an essential requirement for patient outcomes. Undocumented migrants fall below the health systems radar, not being officially eligible for the receipt of care, often reaching emergency departments or health-related NGO's, where they can receive treatment free-of-charge. Neither of which however possessing the necessary expertise in the management of these complex diseases. Thus, it is more likely for such patients to develop medical complications that without timely and appropriate management in an expert multidisciplinary care setting, will quickly result in health deterioration. Moreover, specialized monitoring tests are variably covered by the responsible paying bodies (*e.g.* insurance). For example, MRI for the measurement of iron overload, an essential monitoring test for the early detection and prevention of iron damage to vital organs with great impact on patient survival[22] is available in reference centers in Austria, Germany, France and Sweden but not always reimbursed by paying bodies. Furthermore, the absence of the service in the periphery makes the need for patients to visit reference centers, at least annually, imperative.

National guidelines, developed based on TIF's International Guidelines for the Clinical Management of Transfusion Dependent and Non-Transfusion Dependent Thalassemia, adapted to national circumstances, exist in France, Germany and Sweden. Furthermore, a shared language allows Austrian physicians to refer to German published guidelines. Nonetheless there is diverse awareness about the existence of national guidelines by treating physicians across each country. This is evident by consistently lower than recommended pre-transfusion hemoglobin levels in many patients, especially in adult clinics. Moreover, many patients transfused in peripheral centers, present for transfusion when they feel the need (pallor, fatigue) rather than in accordance to protocol. In addition, in some cases, wrong doses of chelating agents were also reported by patients.

Organized multidisciplinary follow up and management of complications is an essential component for the improved survival of patients.[18,23,24] In view of the lifelong effects on the heart, liver, kidneys, endocrines and other organs, specialists from several disciplines are expected to contribute to the holistic care of patients by providing both early detection and complication management. This of course should be done by specialists who have become familiar with the hemoglobin disorders, and are in communication and complete collaboration with the hematology team, taking common and agreed upon therapeutic decisions and where possible sharing patient visits and communication. In the centers visited in the course of this study, such organized teams were found in only in two adult centers - one in France and one in Germany, and one pediatric center in Austria. In general, patients are referred to specialists once they have developed a complication, while visiting specialists from an early age and before a '*fait accompli*' was found to be rare. Even though the concept of reference centers, as mentioned above is a recognized concept in Europe, actual networking in a shared-care relationship with the periphery where patients may be receiving their routine care, has not been formalized. Despite this, patients have mentioned to the TIF teams that on their initiative they do go to visit a reference center occasionally.

Disease-specific registries, endorsed by the national health authorities were identified in France[8] and Germany.[11] More specifically, the French National Registry covers both thalassemia and SCD whereas in Germany the registry is for SCD while for thalassemia it is in the early stages of functioning. The French National Thalassemia Registry constitutes a best-practice example in Europe, demonstrating the value of developing national disease-specific registries as a service planning tool, as it clearly shows the increasing numbers of thalassemia patients living in the country (and therefore increasing requirements of the healthcare system). Indeed a total of 287 individuals were registered in 2008; 479 in 2010; 515 in 2012 and 666 in 2019.[9] Austria, Sweden and Serbia did not have nationally endorsed disease-specific registries for hemoglobin disorders.

Notably early on in the study it became apparent that health and other services provided for thalassemia overlapped with those provided for SCD, as both disorders are part of the haemoglobinopathy family. Therefore, recommendations and subsequent actions included both disorders, which despite their distinct and different pathophysiology are treated in the same centers, often by the same physicians. In fact, this overlap in services leads patients with both disorders also to face some of the same challenges, as a result not only due to their rarity in the specific countries which are the focus of this study, but also as a consequence of the distinct difficulties faced by migrant communities in general.

Discussion

Migration has changed the local prevalence of both inherited and acquired diseases,[25] and the chronic disorders are a particular challenge. The countries selected for the purposes of the THALIA program were selected as representing the effects of recent migrations and to explore the question whether Europe is ready to meet the medical, social, economic and public health challenges associated with hemoglobin disorders. Acknowledging robust health infrastructure in most of the EU countries, the concept of chronicity with multiple and cumulative organ damage and the need for secondary prevention has not entered the clinical practice of managing these patients who after all are suffering from rare conditions, little known in the host country. However, many other rare congenital red cell disorders are managed by hematologists in Europe, which are met in the indigenous populations that they serve. Is the management of Diamond-Blackfan syndrome, for example, so vastly different from that of beta thalassemia? Could the weaknesses that healthcare systems demonstrate not be due to the sudden increase in cases, but a result of a general weakness in the attention given to the so-called 'benign' as opposed to malignant blood disorders? Could the issue of ethnicity be an additional factor in the provision of expert care?

Europe has long recognized the needs of rare diseases, developing policies and services, such as the creation of registries and the development of European Reference Networks (ERNs).[26,27] In addition, there are numerous centers of excellence and pioneers in research in many European countries. Experts are aware and are considering improvements and actions in critical areas.[28] Despite this, haemoglobinopathy patients do not, in many cases, benefit from the expert care that their new place of residence can provide, thus achieving maximal survival and quality of life. Experience from the visits of TIF teams, indicates an uneven availability of expert help. This is less related to the provision of adequate and safe blood transfusion and the availability of essential medications, but to expertise in their appropriate and timely use. As a consequence, low pre-transfusion hemoglobin and high iron loads were observed. Likewise worrying was the poor performance in providing timely and coordinated multidisciplinary care. These negative impressions were confirmed by patients who generally felt isolated, with little support from organized support groups. These findings are in line with other rare diseases, which face similar issues in the provision of early diagnosis and optimal care.

Hemoglobin disorders however are dis-

tinguished from other rare diseases only in that they are more recently *imported* by migrations. The conclusion then is that they should be provided with all European provisions for rare diseases with the addition of more intense awareness raising and more education of healthcare professionals and the migrant families. In addition, the socioeconomic problems that arise when a family arrives in a new environment, a new culture and a health system that has intricacies to which they must become familiar with, deserves particular attention. Furthermore, the creation and empowerment of patient groups in these countries in an effort to provide peer-to-peer support, present their own distinct challenges directly related to the heterogenous cultural, linguistic, religious, social, educational backgrounds of the migrant communities in which these disorders are found within the host country. This is a stark difference to the homogenous communities that set up powerful patient groups in EU countries with a high prevalence in the indigenous population (*e.g.* Cyprus, Greece, Italy).

The onus of providing quality care rests with healthcare authorities as well as the treating physicians, since chronic and rare conditions require organization of services. The requirement is not necessarily to create specialized haemoglobinopathy clinics where few patients exist, but to incorporate them into benign hematology clinics including day transfusion units, separate from patients with malignant conditions receiving chemotherapy for obvious reasons. Moreover, networking, with adequate planning and support, does not seem to be effective as yet, and the referral relationship between the expert and the physician who sees one or two cases, is not yet an estab-

Table 6. Actions taken in the THALIA Work Program (2018-2020) for meeting challenges and unmet needs of hemoglobin disorders.

1. Policy-Makers:

- Thalassemia EU Health Record: Continuing to monitor the epidemiology of hemoglobin disorders in Europe, an example of which is the Italian WEBTHAL clinical database.30
- Advocating for the rights of patients with thalassemia and migrants in the EU through meetings with the EU Health Commission and health authorities of Greece, Cyprus and Italy (2020).
- Connecting with international bodies, national health authorities and foreign relations envoys to highlight the relation of thalassemia in the EU and migration (2018-2020).
- EU Policy Recommendation & National Charter of Priorities: Comprehensive documents outlining the challenges faced by patients and identifying opportunities for policy changes at the EU and national levels.
- Participation in EU Health Program High Level Conference (2019) to inform and raise awareness about THALIA, thalassemia, SCD, migration and the impact on health infrastructure.

2. Patients & Families:

- Thal e-course: an online interactive educational platform providing disease-specific information as well as information on relevant policies and recommendations for advocacy purposed. Available in English, French, German, Greek, Italian, Arabic and Turkish.
- Train-the-Trainers Capacity Building Workshop for Patients' and Patient Associations (Thessaloniki, 2018; Hamburg, 2019; Virtual, 2020)
- THALIA Mobile Application: launched in 2020, aiming to improve self-management.
- Exchange of best practices through twinning programs (Cyprus/France, 2018; Greece/Germany, 2019).
- Educational webinars (4 in total) on disease-specific issues for thalassemia and SCD.
- Creation of TIF's European Patient Advocacy Group for Thalassemia & Sickle Cell Disease. Total meetings organized: 3.
- Clinical Trials Update: A digest provided to patients/parents every two months on the latest developments regarding clinical trials in the field (2018-2020).
- Support and provision of technical expertise to patient organizations through empowerment (v. France, Germany), establishment (v. Austria) and mobilization (v. Sweden).
- Publication of brochures on Gene Therapy, Bone Marrow Transplantation & Prevention of Inherited Disorders (2018-2019).
- Thalassemia from A-Z: a comprehensive e-glossary for patients with thalassemia (2019).
- Development of resources for COVID-19 and hemoglobin disorders including information about the effects of SARS-CoV-2 on patients, blood transfusion, Sickle Cell Disease, Vaccines and Therapeutic Drugs, etc. (2020).

3. Healthcare professionals:

- eThalEd e-course: an online course on the clinical management of thalassemia. Available in English, French and Arabic.
- e-SCD course: an online course on the clinical management of SCD (2020).
- Guidelines for the Clinical Management of Non-Transfusion Dependent Thalassemia. Available in English and French (2018).
- Guidelines for the Clinical Management of Transfusion Dependent Thalassemia. Updated 4th edition (In print).
- Short Guide for the Clinical Management of Transfusion Dependent Thalassemia. Distribution across Europe.
- High Level Summit for Healthcare Professionals (Thessaloniki, 2019).
- Symposium for Healthcare Professionals in Europe (Virtual, December 2020).
- Renzo Galanello Fellowship. Training of 5 physicians (2018-2020).
- Educational webinars (7 in total) on various aspects of thalassemia clinical management (2020).
- Development of resources for COVID-19 and hemoglobin disorders including a Haemoglobinopathy Patient Pathway (Available in English and Greek) and Risk Classification (2020).
- Raising awareness among EU health professionals through participation in Annual Congress of European Hematology Association (2018-2020), International Society for Blood Transfusion (2018), European Association for the Study of Liver (2019).

4. General Public:

- Publication and dissemination of awareness raising posters on Migration and brochures on Prevention of Inherited diseases: -thalassemia.
- Articles in press and interviews regarding thalassemia, migration and Europe.
- TIF website: Updating daily with news. Available in English, French, German, Greek, Italian, and Arabic.
- Training of European Solidarity Corps volunteers from Germany, France and Italy about hemoglobin disorders and the migration of populations from high prevalence areas to Europe as refugees, political asylum seekers and economic migrants (2019-2020).

lished practice in many locations. The beliefs by many hematologists that these blood disorders, due to their benign nature (as opposed to malignant hematological diseases) are simpler in their management, and merely entail the provision of blood and medications, is an unfortunate common perception.

A country that stands out in the European setting is the UK. In this country for many decades populations from the commonwealth countries have been settling and are now in second and third generation. This has led to planning of reference centers and commissioning, especially located in areas where these communities live, networking, quality control of centers with annual reviews, registries, research, national guidelines on all aspects of clinical management, including psychosocial support. Finally, a national prevention program based mainly on antenatal clinic and neonatal screening, prenatal and pre-implantation genetic testing.[29] This kind of comprehensive planning is expected be followed by all European health services as these conditions become more visible.

The THALIA Work Program (2018-2020) has enabled, as demonstrated in this study, to identify the location of patients with hemoglobin disorders as well as to further understand the challenges met by both patients and healthcare professionals in the receipt and provision of quality healthcare respectively. In addition to this situation analysis, the THALIA Work Program facilitated the implementation of corrective measures to alleviate the challenges identified through activities listed in Table 6.[30]

Conclusions

Improving case management and developing a culture to focus on rare and chronic disorders, which are recently appearing in the spectrum of clinical experience of local specialists, is a challenge. The organization of healthcare services for *unfamiliar* conditions to the authorities, raising awareness to a health burden which is now increasing, requires a resilience in health service management, when concerns over adequacy of budgetary support are paramount. The fact that poor monitoring and treatment now will increase complications and costs over time is not known to many services. Change in some settings takes time, especially where a culture of networking and collaborative care is a necessity. Such networking is possible because centers of expertise do exist in most European countries. The management of hemoglobin disorders shares the same difficulties with other rare conditions in Europe. Additional issues arise because the conditions are recently *imported*, and the social considerations of immigrant populations. Nonetheless, there is ample international expertise and knowledge to be offered for the appropriate clinical management and care of patients with hemoglobin disorders, that would guarantee an improved quality of life.

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