Volume 3 Number 1
January 2023
Editor: G. SOTTILOTTA
Editor in Chief: D. GRECO MALARA

ONLINE JOURNAL OF

HEMATOLOGY & MEDICINE

OJHM

https://www.hemonline.it
e-mail: ojhm@hemonline.it

ONLINE JOURNAL OF HEMATOLOGY AND MEDICINE

Aims and scope

ONLINE JOURNAL OF HEMATOLOGY AND MEDICINE (OJHM) is an interdisciplinary open access online journal focusing primarily on blood diseases. The journal publishes original contributions in non-malignant and malignant hematological diseases. It also covers all the areas related to the hematological field that takes care of diagnosis and treatment of blood disease. Particular editorial interest is addressed to: Inherited and Acquired Clotting Disorders, Antiphospholipid Syndrome, Clinical Management of Bleeding Diseases, Coagulopathies, Hemophilia, Platelets Disorders, Thrombotic Disorders. Manuscripts should be presented in the form of original articles, editorials, reviews, short communications, or cases report, all submissions are rigorously peer reviewed.

All manuscripts submitted to OJHM must be previously unpublished and may not be considered for publication elsewhere at any time during OJHM's review period.

Contents

Berardino Pollio[1]
Paola Saracco[2]
Irene Ricca[1]
Teresa Ceglie[2]
Claudia Linari[1]
Roberto Albiani[1]

[1] Transfusion, Medicine Service, Regional Reference Center for Hemorrhagic and Thrombotic Diseases in Children. Regina Margherita Children Hospital, Città della salute e della scienza di Torino, Italy
[2] School of Pediatrics, University of Turin (Italy)

ONLINE JOURNAL OF HEMATOLOGY & MEDICINE
Editor: G. Sottilotta
Editor in chief : D. Greco Malara
e-mail: ojhm@hemonline.it
https://www.hemonline.it

Case Report

Severe hematomas in an inherited FXIII deficiency successfully treated with Catridecacog (rFXIII-A)

Abstract.

A Pakistani boy with an inherited FXIII deficiency came at our attention with a suspect of compartment syndrome, and was successfully treated with recombinant r-FXIII-A replacement. We would like to emphasize the efficacy of rFXIII-A, compared with fresh frozen plasma and cryoprecipitates, which did not cause a significant increase in FXIII levels in our patient. In 2017, our experience had already showed that Catridecacog could be used safely and effectively not only for continued prophylaxis but also for on-demand treatment and adds to the limited body of evidence currently available on rFXIII-A for acute bleedings.

Keywords: inherited FXIII deficiency, FXIII, rFXIII-A, Catridecacog, hematomas, bleeding disorders

Introduction

Factor XIII (FXIII) is a protransglutaminase that, after activation by thrombin and in the presence of calcium, becomes transglutaminase, leading to increased stability of the fibrin clot. Plasma FXIII is a heterotetramer composed of 2 catalytic A-subunit and 2 carrier B-subunits linked by noncovalent bonds [1]. Inherited FXIII deficiency is a rare bleeding disorder caused by defects in both FXIIIA and FXIIIB genes; however, the majority of the cases are attributed to genetic variants of the FXIIIA gene. The clinical symptoms of FXIII deficiency include delayed wound healing, recurrent spontaneous miscarriage, bleeding of soft and subcutaneous tissue, and life-threatening spontaneous CNS bleeding, which is the primary cause of death in affected patients. The treatment of FXIII deficient patients consists of the use of fresh frozen plasma, cryoprecipitate, plasma derived concentrate or the recently developed recombinant FXIII (r-FXIII-A) for patients with FXIIIA subunit deficiency [2].

Report of the case

Here we report the case of a 14-year-old Pakistani boy with an inherited FXIII deficiency who came at our attention with a suspect of compartment syndrome, successfully treated with recombinant r-FXIII-A replacement. In 2017, he was referred to our Hospital because of a huge hematoma on the lower left limb and the suspicion of a compartment syndrome. In the familiar history, the consanguinity of his parents was noted. The boy had a history of bleeding after circumcision. At that time, he was transfused in his native country with HCV infected whole blood coming from his father. He was discharged with an undefined diagnosis of bleeding disorder. Other two severe bleeding episodes have been reported after traumatic events on the left hand and lips. When he was 10-year-old, he moved to Italy. During this period in Italy his father asked the paediatrician for a haematological counselling. However, as first level coagulation tests

treatment period. Unfortunately, two months after the suspension of the prophylaxis the patient had a contralateral post-traumatic intramuscular hematoma while he was playing soccer. Once again, he was treated with r-FXIII-A with excellent response. At the last follow-up, he was in good physical conditions the hematoma was undetectable, and he was still carrying on a secondary prophylaxis with r-FXIII-A at 2500 U ev every six weeks. this dosage is slightly different from that indicated in the technical data sheet but allows to avoid the waste of residual drug in the vial.

Discussion

Congenital FXIII deficiency is a rare autosomal recessive bleeding disorder whose diagnosis is challenging due to the rarity of the disease and because the standard clotting tests such as prothrombin time, activated partial thromboplastin time, fibrinogen level, platelets count and bleeding time result normal.

It is a disease difficult to manage, independently of the diagnosis because of a heterogeneous clinical presentation, as showed by the EN-RBD study [3]: patients with FXIII coagulant activity levels <30% might bleed with a heterogeneous clinical presentation. In particular, those with low activity levels developed spontaneous major bleeding and spontaneous minor or post traumatic bleeding. Then, a cut-off level of FXIII coagulant activity that could discriminate patients with severe bleeding manifestations from those with minor or no bleeding has been searched and The Prospective Rare Bleeding Disorders Database showed that a level of 15% FXIII clotting activity could be a good therapeutic target to maintain in patients with no bleeding [4].

The severity of bleeding symptoms in congenital FXIII deficiency is the main reason for regular replacement therapy. Prophylaxis is highly efficient and successful because of the long half-life of FXIII. Fresh frozen plasma, cryoprecipitate, and a plasma-derived, virally inactivated FXIII concentrate have been available for prophylaxis. Moreover, the new recombinant FXIII manufactured in Saccharomyces cerevisiae is now available. The r-FXIII-A links in plasma with the endogenous FXIII-B subunit to form stable FXIII heterotetramer. FXIII-B-subunit deficiency is associated with a much more reduced half-life of the administered pharmacologically active A-subunit.

The efficacy and safety of the new rFXIII-A was shown in 2012 in a multinational prophylaxis trial demonstrating that a single dose of 35 UI/kg r-FXIII-A maintained plasma FXIII levels above 10% in patients aged ≥ 6 years and with FXIII A deficiency.

In our case, given the unavailability of plasma-derived FXIII and the low levels of FXIII after cryoprecipitates, r-FXIII-A was administered as treatment and then every 4 weeks as prophylaxis during physiotherapy, monitoring his trough levels closely, in order to maintain it higher than 30%.

This strategy allowed to resolve the acute bleeding and prevent invalidity due to muscular damage related to bleeding.

The subunits A and B were not tested before the use of r-FXIII-A, but retrospectively we can say that the boy has an A defect, because of the improvement in FXIII activity measured after r-FXIII-A replacement.

It remains unclear if our patient, that is still carrying on a secondary prophylaxis with r-FXIII-A, will need a long-term prophylaxis.

In 2017, recombinant FXIII-A was indicated only for the long-term prophylaxis of bleeding in patients with type A subunit defect, but this case shows the successful use of recombinant FXIII-A as treatment of acute hemorrhagic episodes in an inherited FXIII deficiency.

The on-demand treatment has not been studied in the clinical development programme but, recently, the on-demand use has been reported in the drug data sheet of Catridecacog.

In this report, we would like to emphasize the efficacy of rFXIII-A, compared with fresh frozen plasma and cryoprecipitates, which did not cause a significant increase in FXIII levels in our patient.

In 2017, our experience had already showed that Catridecacog could be used safely and effectively not only for continued prophylaxis but also for on-demand treatment and adds to the very limited body of evidence currently available on rFXIII-A for acute bleedings.

were found normal, the paediatrician considered any further investigation unnecessary. In October 2017, the patient was referred to a peripheral hospital because of a painful swelling on his lower left limb after a trauma on the bike. Knee radiography was normal, while a hematoma in gastrocnemius muscle of 4 cm diameter was detected on a Doppler ultrasound. After hematological consultation, FXIII dosage was requested. However, almost a week passed between sample collection and results availability; during this period the hematoma progressively enlarged because no specific treatment was started in the absence of a diagnosis. On the physical examination the patient showed hyperpyrexia (TC 39,5 °C), painful swelling on the left knee, leg and proximal calf with red and hot skin. A severe functional limitation in the dorsal flexion of the foot with a tendency to equinism was noted. Increased inflammation and muscle lysis indexes (RCP 15.4 mg/dL, CPK 1243 U/L) were also detected. As soon as the result of FXIII dosage was available (10,7%), the patient was treated with fresh frozen plasma (FFP) at the dosage of 20 ml/kg, as the FXIII concentrate was at that time not available, and then he was referred to our hospital.

At our examination he was still feverish. The left calf circumference was 37 cm. Obliged decubitus with left limb in flexion was noted. Sensibility was not impaired and peripheral pulses were detectable. An echocolordoppler showed a regular arterial flow. A multidisciplinary team including an orthopaedic, a physiotherapist, an infectious disease specialist and a hematologist took care of him in order to avoid the development of a compartment syndrome. On October 20th, 2017, after infusion of FFP the result of FXIII dosage was 17,6% (2:30 p.m.)

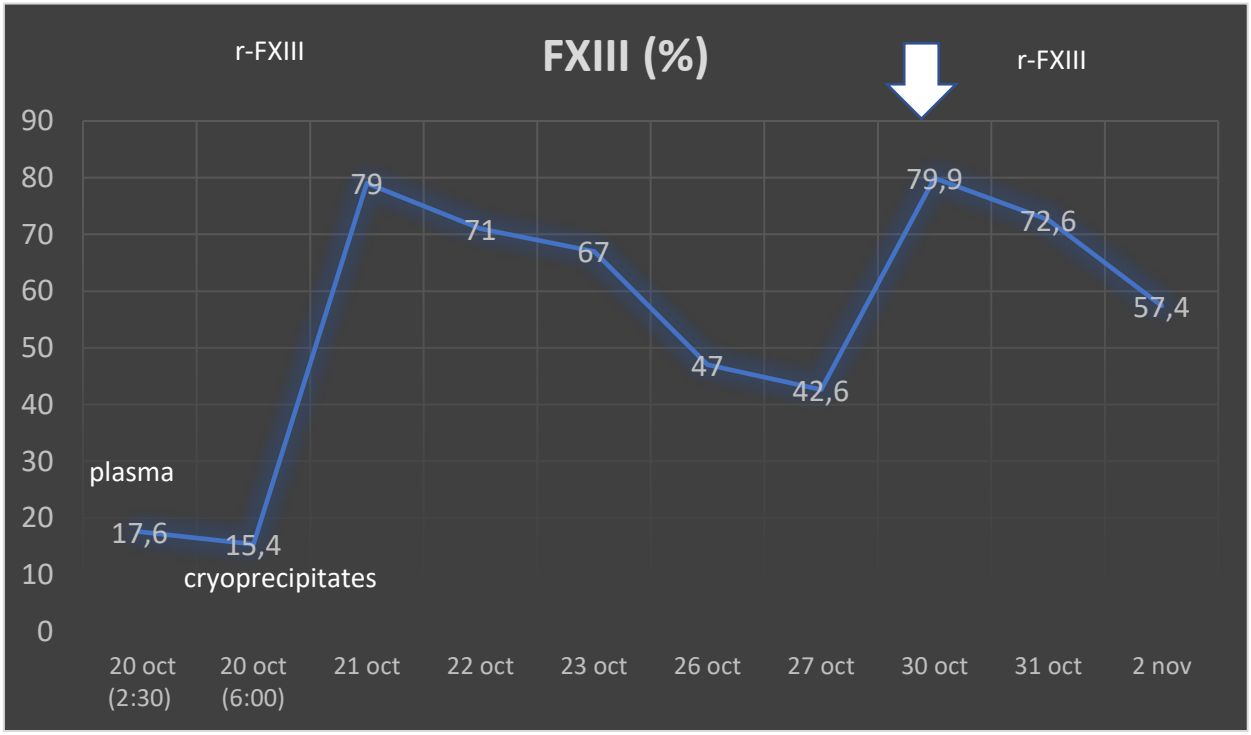


Figure 1: Dosage of FXIII levels (%) after infusion of fresh frozen plasma, cryoprecipitates

The patient was at first treated with cryoprecipitate (4 bags) and then, because of persistent low levels of FXIII (15,4% on October 20th, 2017 at 6 p.m.), with r-FXIII-A replacement at the dosage of 50 U/kg.

FXIII levels were near 80% immediately after r-FXIII-A replacement and they still remained > 60 % in the following 48 hours (figure 1). Ten days later the clinical conditions of the patient were definitely better: he was afebrile, the inflammatory indexes were almost normalized and no more pain at rest was reported. The calf circumference was 32 cm (the other calf measured 29 cm) with normal skin. He had almost recovered the mobility of the leg. The hematoma measured 15 x 8 mm. In order to keep FXIII levels higher than 30%, a secondary prophylaxis with r-FXIII-A was administered monthly for 6 months during the physiokinesitherapy

References

1) Inbal A, Oldenburg J, Carcao M at al. Recombinant factor XIII: a safe and novel treatment for congenital factor XIII deficiency. Blood. 2012;119(22):5111-5117.
2) Peyvandi F, Menegatti M. Treatment of rare factor deficiencies in 2016. Hematology. 2016;(1);663-669.
3) Peyvandi F, Palla R, Menegatti M et al. European Network of Rare Bleeding Disorders Group. Coagulation factor activity and clinical bleeding severity in rare bleeding disorders: results from the European Network of Rare Bleeding Disorders. J Thromb Haemost. 2012;10(4):615-621.
4) Peyvandi F, Palla R, Menegatti M et al. Minimal residual FXIII coagulant activity to prevent spontaneous major bleeding, on behalf of the PRO-RBDD group. Haemophilia. 2016;22(suppl4):17.

Acknowledgments

The authors acknowledge Alessandra Di Lelio and Antonio Nicolucci (CORESEARCH S.r.l.- Center for Outcomes Research and Clinical Epidemiology, Pescara, Italy) for their support in medical writing and editorial assistance.

Funding

The authors stated that they had no interests which might be perceived as posing a conflict or bias.
The editorial assistance was provided by CORESEARCH S.r.l. through a Novo Nordisk S.p.A. unconditional grant. The authors of the publication are fully responsible for the contents and conclusions. Novo Nordisk S.p.A. did not influence and has not been involved in the data interpretation presented in the manuscript.

Corresponding author

Dr. Berardino Pollio. Service of Transfusion Medicine Service, Regional Reference Center for Hemorrhagic and Thrombotic Diseases in Children. Regina Margherita Children Hospital, Città della salute e della scienza di Torino, Italy. E-mail: bpollio@cittadellasalute.to.it

Gianluca Sottilotta[1]
Gaetano Giuffrida[2]

[1]UOSD Microcitemie Emostasi e Trombosi, Grande Ospedale Metropolitano di Reggio Calabria (Italy)

[2] Centro di riferimento regionale per la prevenzione, diagnosi e cura delle malattie rare, Divisione di Ematologia Haematology, A.O.U Policlinico - S. Marco, Università degli studi di Catania, (Italy)

ONLINE JOURNAL OF
HEMATOLOGY & MEDICINE

Editor: G. Sottilotta
Editor in chief: D. Greco Malara
e-mail: ojhm@hemonline.it
https://www.hemonline.it

G. Sottilotta, G. Giuffrida

IX INTERREGIONAL CONFERENCE. NEW CHALLENGES IN THE MANAGEMENT OF CONGENITAL AND ACQUIRED BLEEDING DISORDERS: FROM NEW THERAPIES TO THROMBOTIC COMPLICATIONS

The evolution of the therapeutic management of congenital and acquired haemorrhagic coagulopathies have reached levels that were unthinkable until a few years ago; especially as regards hemophilia: the forthcoming marketing of gene therapy and the new non-substitutive subcutaneous therapies and the latest concentrates, with a much longer half-life than the available products we have had in the last 20 years, has changed the way of "thinking" the treatment of these pathologies; especially as regards the haemostasis laboratory which, above all in the latest period, was characterized by the loss of its identity: this was due to the centralization of hospital laboratories and the lack of personnel with experience in the field of coagulation; now we are facing new realities where pharmacokinetics is carried out more and more rarely, also due to the diffusion of non-substitute therapies, whose laboratory evaluation, useful but no longer indispensable, is complex and not feasible except by a few laboratories. These innovations, however, have undeniably made it possible to improve the quality of life of our patients, maintaining therapeutic efficacy and above all, they have allowed us to aspire to objectives, first of all the prevention of joint complications, in a much more efficient way than to what has been done in the recent years. The fruit of all this is what we can see now: the increase in the average life span of the patient and access to all kinds of work, sports and social activities, which are absolutely no different from the general population. The increase in life expectancy, in particular, has forced haemophilia centers to take into consideration thrombotic and cardiovascular pathologies which, although this happens more rarely, also occur in adult and elderly patients with severe haemorrhagic coagulopathy. It therefore appears necessary to organize educational medical events which allow participants to update their knowledge by turning their attention not only to anti-haemorrhagic therapies but to a broader picture concerning the management of haemocoagulative emergencies at 360°, not only congenital but also the acquired ones that may require multidisciplinary skills until the problems have been resolved. So again, this year the Interregional Conference, now at its ninth edition, has as its target the improvement of a global treatment system which concerns not only pharmacological therapy itself, but involves, in addition to the haematologist, numerous professional figures, from orthopedics, to the infectious disease specialist, from the physiatrist to the psychologist, from the nurse to the biologist and the physiotherapist. Traditionally, the second part of the conference was dedicated to associations, that fundamental part of voluntary work which includes families as a social entity most involved from a welfare and therefore

psychological point of view. First of all, the patient and family associations have the objective of affirming the rights of those who, being affected by a rare disease, are forced to deal daily with the problems linked to the disinformation of the institutions at various levels; they are also aware of the necessity to avoid the cuts in health care, to which the citizen has now been forced get used to, especially by the pandemic emergency, affecting not only the quality of medical assistance but also the availability of the treatments themselves. The purpose of the IX Interregional Conference of the Associations, held in Catania (Italy) from 3rd to 4th of December 2022, was therefore to inform and update all those health professionals who may have to deal with coagulopathic patients or with acquired bleeding emergencies during their professional activity on the methods of treatment and approach to various clinical, pharmacological, administrative and social problems. The meeting between the associations aimed to take stock of the current health situation, from the patient's point of view, to improve the management strategies of doctor-patient relationships, and between patients and institutions.

Pier Mannuccio Mannucci
IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre, Milan (Italy)

ONLINE JOURNAL OF HEMATOLOGY & MEDICINE
Editor: G. Sottilotta
Editor in chief: D. Greco Malara
e-mail: ojhm@hemonline.it
https://www.hemonline.it

P.M. Mannucci

HEMOPHILIA AND THROMBOSIS

With the striking advances in hemophilia care that have materialized in the last few decades, an increasing number of persons with hemophilia (PWH) have achieved a quality of life and life expectancy very close to that of unaffected individuals. With ageing, a growing number of PWH develop age-related co-morbidities, including cancer, thrombosis and cardiovascular diseases. The latter (particularly coronary artery disease and atrial fibrillation), represent a new challenge for the hemophilia treatment centers because their management implies a delicate balance between the thrombotic risk and the bleeding tendency, that is further enhanced by the concomitant use of antithrombotic agents. Because evidence from clinical trials is lacking, the management of PWH with cardiovascular diseases and atherothrombosis is mostly based on expert opinions, personal experiences and the adaptation to them of the evidence stemming from studies on people without hemophilia.

Ezio Zanon
Haemophilia Center, General Medicine, Padua University Hospital, Padua (Italy)

ONLINE JOURNAL OF HEMATOLOGY & MEDICINE
Editor: G. Sottilotta
Editor in chief: D. Greco Malara
e-mail: ojhm@hemonline.it
https://www.hemonline.it

E. Zanon

FACTOR XIII DEFICIENCY: CLINICAL MANIFESTATIONS AND TREATMENT

Background: FXIII deficiency is a very rare coagulation disorder. Bleeds are usually muscular or mucocutaneous, but bleeding from umbilical cord at birth and intracranial hemorrhages (ICHs) can occur in cases of severe disease. Plasma-derived concentrates (Fibrogammin®) and RFXIII concentrates (Novothirteen®) can be used on demand to control the bleeding. The best treatment in patients with severe disease is the use of plasma-derived or recombinant FXIII concentrates on prophylaxis at the dose of 10-26 IU/kg every 4-6 weeks and 35 IU/kg every 4 weeks, respectively. Few data on the use of rFXIII in the real-world scenario are available.

Material and methods: recently we enrolled all patients presenting FXIII deficiency treated with catridecacog at ten Italian Hemophilia Centers. PK-profiles were evaluated and clinical data and outcomes were collected and analyzed.

Results: overall 20 patients with FXIII deficiency were enrolled, 75% presenting severe disorder. 11/20 were females. Mean age at diagnosis was 15 years (range: birth-74 years). 60% had a known family disorder. Pharmacokinetics was assessed in 18/20 of cases before starting prophylaxis. Mean age at PK-evaluation was 36.4 years (6-74 years), mean dose of drug infused for PK was 33.9 IU/kg (25-50 IU/kg). Prophylaxis was subsequently started on 65% of patients at a mean dosage of 33.8 IU/kg (range 25.0-80.0 IU/kg), on average every 4.0 weeks (range 3.0-8.0 weeks). During an average follow-up of 43 months, one ileo-psoas hematoma which quickly resolved, one muscular hematoma, and two minor surgeries were reported. One severe patient who remained on demand treatment experienced a severe intracranial hemorrhage.

Conclusion: efficacy and safety of prophylaxis with catridecacog was proven in all patients, also in preventing severe bleeding. The cumulative PK profile was similar to that reported in the MENTOR studies, but dosage and infusion timing for each patient were in some cases very different.

Luana Fianchi
Dipartimento di diagnostica per Immagini, Radioterapia Oncologica ed Ematologia
Fondazione Policlinico Universitario A. Gemelli, IRCCS-Rome (Italy)

ONLINE JOURNAL OF
HEMATOLOGY & MEDICINE
Editor: G. Sottilotta
Editor in chief: D. Greco Malara
e-mail: ojhm@hemonline.it
https://www.hemonline.it

L. Fianchi

THROMBOTIC MICROANGIOPATHIES: THROMBOTIC THROMBOCYTOPENIC PURPURA VS ATYPICAL HEMOLYTIC UREMIC SYNDROME

Thrombotic microangiopathies (TMAs) are rare and life-threatening diseases. In recent years, there have been major advances in understanding the pathophysiology, classification, and treatment of these disorders, including the introduction of new drugs. Early differential diagnosis is crucial for prompt treatment to reduce high mortality rates and late organ damage. The classic forms of thrombotic microangiopathy are thrombotic thrombocytopenic purpura (TTP), typical hemolytic uremic syndrome (HUS) associated with toxin-producing bacteria, atypical HUS (aHUS) due to dysregulation of alternative complement C3 convertase attributable to genetic causes, and HUS secondary to coexisting disease. The hallmark of TMA is the association of microangiopathic hemolytic anemia, detected by positive schistocytes in peripheral blood smears, with thrombocytopenia and organ changes, that may vary and be more or less pronounced depending on the TMA subtype. TTP is caused by an acquired or congenital deficiency of the von Willebrand factor-cleaving protease ADAMTS-13. Determination of ADAMTS13 activity and ADAMTS13 inhibitors are critical for differentiating TTP from other TMAs. This presentation will specifically focus on the differential diagnosis between TTP and aHUS, their clinical management and the different therapeutic approaches.

Orazio Di Gregorio
Lead HCP and Nurse Coordinator
Healthcare Network Partners Italy

ONLINE JOURNAL OF HEMATOLOGY & MEDICINE
Editor: G. Sottilotta
Editor in chief: D. Greco Malara
e-mail: ojhm@hemonline.it
https://www.hemonline.it

O. Di Gregorio

THE ROLE OF THE NURSE IN THE HOSPITAL AND HOME MANAGEMENT OF THE HEMOPHILIAC PATIENT

The transformation of haemophilia from a life-threatening disease into a long-term manageable condition is changing the role of the haemophilia nurse specialist. It will likely be less clinically focused and have a greater emphasis on psychosocial support, including motivation, shared decision-making, support and self-advocacy for patients. Placing the person in all his complexity at the center of the treatment process is the main objective that the entire health system must achieve: it is no longer possible to reason in pharmacocentric terms, but the patient's needs must be given priority. It is important to introduce valuable services, such as patient support programs, aimed at significantly improving the quality of life of the patient and of those who assist him and which, at the same time, involve and respond to the needs of the clinician who remains the primary reference for the patient.

Within these support programs, the contribution of the community nurse is particularly important at key moments in the patient and family journey, such as immediately after diagnosis, when prophylaxis is started, during joint health monitoring and in pharmacokinetic studies up to the teaching of self-infusion. Better diagnosis and comprehensive care have increased lifetime utilization and reduced bleeding rates and joint impairment for people with hemophilia. There is now much more emphasis on preventing major bleeding and teaching and supporting self-management. Models of haemophilia care are evolving and specialist nurses will play a leading role in their implementation. The revolution in haemophilia care presents exciting opportunities and challenges for nurses engaged in haemophilia, and there is ample scope to find different ways to deliver nurse-led care. Hemophilia nurses need to look beyond their own hospital or hemophilia center and share research and best practices with fellow nurses nationally and globally to improve the care they provide

Gianluca Sottilotta
UOSD Microcitemie Emostasi e Trombosi G.O.M. «Bianchi-Melacrino-Morelli» Reggio Calabria
(Italy)

ONLINE JOURNAL OF
HEMATOLOGY & MEDICINE
Editor: G. Sottilotta
Editor in chief: D. Greco Malara
e-mail: ojhm@hemonline.it
https://www.hemonline.it

G. Sottilotta

PROPHYLAXIS IN VON WILLEBRAND DISEASE PATIENTS

Von Willebrand disease (VWD) is the most common inherited bleeding disorder resulting from a deficiency or dysfunction of von Willebrand factor (VWF). VWF has an integral role in hemostasis because it binds to and stabilizes FVIII as well as facilitating platelet adhesion to the injured endothelium. VWD has been characterized into three types: type 1, the most common, caused by a partial quantitative deficiency of VWF; type 2 which is observed in approximately 20% of cases and results from VWF dysfunction due to qualitative abnormalities; type 2 VWD has been further subdivided into four subtypes: while type 2A is characterized by a loss of high-molecular-weight VWF, type 2B results from a change in the VWF structure leading to an increased affinity to platelets. Type 2M is caused by a reduced interaction of VWF with platelets, and type 2N results from reduced binding capacity of VWF to FVIII. Type 3, the rarest form, occurs in less than 1% of cases and is due to a virtual absence of VWF.

Individuals affected benefit from care in a comprehensive bleeding disorders program. The two main treatments are desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]) and clotting factor concentrates (recombinant and plasma-derived) containing both VWF and FVIII (VWF/FVIII concentrate). Indirect hemostatic treatments that can reduce symptoms include fibrinolytic inhibitors; hormones for menorrhagia are also beneficial. Individuals with VWD should receive prompt treatment for severe bleeding episodes. Pregnant women with VWD are at increased risk for bleeding complications at or following childbirth. The major symptoms that are present in patients involve mucocutaneous and gastrointestinal bleeding, including epistaxis, easy bruising, as well as provoked bleeding due to injury, surgery, and other invasive procedures, especially dental work. Patients with severe forms of VWD may have frequent haemarthroses, some patients have recurrent gastrointestinal bleeding, often without lesions in the gastrointestinal tract, and need treatment every day or every other day. Finally, there are children who frequently have epistaxis and severely enough to cause anaemia. In these frequent and severe bleeders, the optimal therapy may be regular prophylaxis with VWF/FVIII concentrates rather than on-demand treatment on the occasion of bleeding episodes. A prospective, observational, national post-marketing study, which enrolled patients of all ages and VWD types, was conducted in France from 2004 to 2009. Patients were observed for up to 3 years and treated with a pure VWF concentrate (Wilfactin®) on one or more occasions. Efficacy was assessed for each major event. This study showed that Wilfactin allowed a very high efficacy response in surgery to prevent perioperative bleedings, in curative treatment, and in long-term prophylaxis with no remarkable safety signals. In particular, there were no thrombotic events, even in high-risk patients. In less than half of the cases a priming dose of factor VIII had to be given to obtain the rapid increase in FVIII:C needed in some situations. Wilfactin provided a sound basis for effective and tailored patient treatment across a range of clinical settings.

Gianluca Sottilotta[1]
Dora Messina[2]
Mariana Battazza[1]
Andrea Buzzi[2]

[1] UOSD Microcitemie Emostasi e Trombosi, Grande Ospedale Metropolitano di Reggio Calabria (Italy);
[2] AIMeF (Italy)
[3] Associação Brasileira de Pessoas com Hemofilia (Brasil)
[4] Fondazione Paracelso, Milan (Italy)

ONLINE JOURNAL OF
HEMATOLOGY & MEDICINE
Editor: G. Sottilotta
Editor in chief : D. Greco Malara
e-mail: ojhm@hemonline.it
https://www.hemonline.it

Original Article

Unmet needs and perceived shortcomings due to covid-19 in hemophilia patients

Abstract.

Abstract: The large allocation of human and economic resources to face the pandemic and the lockdown mobility restrictions led the community of persons with haemophilia to be resilient and adaptable, engaging in adopting new methods to ensure their continuity of care. This study aimed to evaluate the emotions which have affected the haemophilia adult patient's daily life, during the first year of pandemic and what behaviors have been adopted to face the socio-economic re-strictions including lockdown, social distancing and self-isolation, as well as the limited access to Hemophilia Treatment Centres (HCT). An 18-item anonymous online survey for adult PWH was translated into four languages and was conducted in 2021, from February to April. The survey revealed that in a condition of social isolation, it is the experience of a sense of uncertainty that prevails, which, although it is not possible to eliminate completely, can however be managed, if continuity in relationships and support is guaranteed even at a distance. The results emerging from our work will be useful in the near future in order to improve professional performance in similar situations, and to optimize the synergy between the HTC doctor and the patient..

Keywords: COVID-19; Hemophilia; pandemic; lockdown; psychological impact

Introduction

Coronavirus disease 2019 (COVID-19) has made a significant impact on the world's health, economic and political systems; as of October 1, 2022, more than 618 million people have been infected worldwide, with over 6.6 million deaths [1] since December 2019, when a series of cases of severe pneumonia was first described in Wuhan-China. The large allocation of human and economic resources to face the pandemic and the lockdown mobility restrictions led to developing strategies to minimize risks of inadequate access to the standard medical care for patients with chronic diseases and/or requiring regular clinical monitoring, like those with congenital bleeding disorders [2]. Redirection of re-sources towards the pandemic and measures aimed at reducing infection risk have limited access to in-person care at Hemophilia Treatment Centres (HTC)[3]. Although home delivery of the clotting factor for self-infusion is standard practice in some countries, in most of them, people must visit pharmacies or treatment centres to pick it up, when available. During the COVID-19 pandemic era this has been more difficult even if there are governments which have adopted factors concentrates home delivery to assure continuity of treatment for people with bleeding disorders [4]. Treatment centres have also had to adapt quickly to prevent disruption in providing consultations, laboratory tests and other services. Telemedicine has been used to maintain contact with patients in some countries and where this was not available other methods have been adopted often thanks to the help of the local bleeding disorder organizations [5,6]. Although the community of per-sons with haemophilia (PWH) has shown to be resilient and adaptable, engaging in adopting new methods to ensure their continuity of care, a large proportion of adults have faced financial struggles due to job losses or suspensions, while children and adolescents have experienced changes in their education and limits on their

social interactions. These multiple challenges have likely had a negative impact not only on PWH's physical health but also on their psycho-social well-being [7]. This study aimed to evaluate the emotions which have affected the haemophilia adult patient's daily life, from different countries, representing a variety of cultural and economic settings, and different health care systems, during the first year of pandemic and what behaviors have been adopted to face the socio-economic restrictions including lockdown, social distancing and self-isolation, as well as the limited access to HTC. Another purpose was to find out possible unmet needs or perceived shortcomings due to Covid-19 in the quality of medical care services, with the aim of understanding how to improve PWH global assistance.

Materials and Methods

An 18-item anonymous online survey for adult PWH was carried out using Google Forms application. It was translated into four languages (English, Italian, Portuguese and Spanish) and was conducted in 2021, from February to April. The study was promoted online using social networks, messaging apps and emails to hemophilia associations world-wide, asking patients to participate voluntarily. The survey consisted of multiple-choice responses and checkboxes. The participants of the study were fully informed about the aim, procedure, and privacy considerations, and an online informed consent was obtained. Data were collected through an 18-question online individual interview composed of five questions about nationality, age, employment, number of inhabitants of residence city, education level, diagnosis, treatment regime, and 12 questions regarding the worries, fears and questions one year after the onset of covid-19 pandemic. The questions on the psychological reaction of patients with hemophilia during lockdowns and possible unmet needs or perceived shortcomings due to covid-19 restrictions, as well as the evaluation about how much and in what way emotions have affected the hemophilia patient's daily life were: “When you learnt of the covid pandemic, were you afraid that your hemophilic condition could somehow expose you to infection more than people without hemophilia?” “What effect did the information provided by the government, health care and local authorities have on you? “Many hemophilia dedicated websites published information and reassurances about hemophilia management during the covid-19 pandemic. Did they help you?” “Did you/do you need medical/psychological support to better address the current situation? If yes, who did you/would you contact?” “In your opinion, may the current situation have psychological consequences in the future, even when the pandemic will be over?” “During the last year, did you happen to experience particular sensations that worried you or made you feel uncomfortable?” “Do you recognize as yours one or more of the following fears?” “Did you find it difficult to manage the relationships with the professionals you need for your hemophilia?” “Which aspect of the current situation has the greatest impact on your health?” “What kind of help do/did you need?” “Have the check-ups and the planned activities at your Hemophilia Center been affected by the pan-demic?” The first question was the agreement to the use of the answers for scientific purposes. The last question was whether or not the person had already had the COVID-19 infection.

Results

Of the 209 PWH who completed the questionnaire, 5 did not provide consent to the use of their responses, so the participating patients were 204 from 24 different countries (36 Spanish-speaking, 47 English-speaking, 40 Portuguese-speaking and 81 Italian-speaking). The age was between 18-30 in 29.8% of cases (63), between 31-50 in 45.5% of cases (96), between 51 and 70 in 22.8% of cases (48) and over 70 in 1.9% of cases (4). About the geo-graphical distribution of the participants: 84 patients were European, 36 Asian, 81 American (Northern: 17, Central: 13, Southern: 51), 3 African. The education level of the participants was: elementary school 9 patients, junior high school 16 patients, high school 90, university degree 86, PhD 3. 17.6% of them said they did not work because unemployed, 18.1 % were students, 30.4% of them worked as clerks, 12.8 % were retired from work, the remaining 21.1 % were freelancers. 64 PWH (31.4%) declared to live in a large city (> 500.000 inhabitants), 83 (40.7%) in a city (> 15.000 inhabitants), 46 (22.5%) in a town

(<15.000 inhabitants) and 11 (5.4%) in a small village (<200 inhabitants). The demographic characteristics are summarized in table 1

Age			Education level			Employment	
18-30	63 (28.8%)		Elementary school	9 (4.4%)		Unemployed/ unoccupied	36 (17.6%)
31-50	96 (45.5%)		Junior high school	16 (7.8%)		Free-lance	43 (21.1%)
51-70	48 (22.8%)		High school	90 (44.1%)		Clerk	62 (30.4%)
>70	4 (1.9%)		University Degree	86 (42.2%)		Retired	26 (12.8%)
			PhD	3 (1.5%)		Student	37 (18.1%)

Table 1: Demographics characteristics of the survey participants (n=204)

With regard to the clinical characteristics: 178 patients reported having haemophilia A (87.3%) and 26 haemophilia B (12.7%), with a prevalence of cases of severe hemophilia in both groups A and B; of these, 12 had inhibitors against FVIII; in relation to the treatments: 121 patients (59.3%) underwent prophylaxis and 83 (40.7%) were treated on-demand. The percentages for prophylaxis patients were different according to the geographical origin: in Italy, for example, 70.4% of the interviewed sample were on prophylaxis, in Central America 44.4% received prophylaxis, while in Africa only 33%. The clinical characteristics of the patients, divided by geographical areas, are summarized in table 2.

Haemophilia type	Total 204	Africa	Asia	Europe	Central America	North America	South America
A severe	117 (57.4%)	3	19	48	6	8	33
A moderate	29 (14.3%)		7	12	2		8
A mild	20 (9.8%)		5	9	1	4	1
B severe	19 (9.3%)		1	7	2	4	6
B moderate	5 (2.4%)		1		2	1	1
B mild	2 (0.9%)		1	1			
A with inhibitors	12 (5.9%)		1	7	1		3
B with inhibitors	0						

Table 2: Health-related and characteristics and provenience of the survey participants (n=204)

Treatment	Total	Africa	Asia	Europe	Central America	North America	South America
Prophylaxis	121 (59.3%)	1	3	59	4	11	43
On demand	83 (40.7%)	2	33	25	9	6	8

Table 3: Anti-haemorrhagic treatment of participants (n=204)

The type of treatment is resumed in table 3. Regarding the questions about emotions and feelings in relation to the pandemic, to question 8, which asked if PWH were afraid that haemophilia makes you more exposed to COVID-19, the sample of people interviewed replied as follows: 47 "not at all" (23.1%), 93 "a little bit" (45.6%), 34 "moderately" (16.6%), 22 "quite a bit" (10.8%), 8 "extremely" (3.9%). About question 9 on the information provided by political and health institutions for which each participant was allowed to give several answers (multiple answers): 42 answered reassured, 76 confused, 15 answered angry, 27 were scared, 9 felt lonely, 35 gave other or combined answers. To question 10, regarding the usefulness of the information obtained from websites dedicated to the haemophilic patient, (also in this case multiple answers were allowed): 62 PWHs answered “yes they made me understand more”, 23 "yes but the fears remained", 8 "yes I understood and I felt reassured”, 97 replied that they had not consulted any site, 14 gave

other answers. To question 11 regarding the need for medical / psychological support to deal with the social restrictions caused by the Pandemic, and what type of support was preferred, the sample of people interviewed replied as follows (multiple choice): 115 who did not need it, 24 replied that they had contacted the family doctor, 5 contacted the public psychology service, 6 contacted a private doctor, 36 contacted their HTC, 18 gave other or combined answers. Regarding question 12, if it was believed that the current pandemic may have psychological consequences in the future, even when this is over, almost half of the people interviewed, 93 (45.6%) answered "yes surely", 32.4% "maybe yes, I don't know", while only 20.1% answered “I don't think so” and 1.9% “Absolutely not”. To question 13, if in the last year they had experienced particular sensations that worried or made them feel uncomfortable, and if they recognized they had experienced one or more fears, (multiple choice allowed), the sample of people interviewed answered thus: 72 experienced "generalized anxiety", 58 "great stress", 69 "Worry about not doing enough to protect myself and my loved ones", 8 "guilt", 20 "excessive anger", 53 "sense of powerlessness", 29 "Intolerance toward people, including relatives", 60 "fear of visiting my Haemophilia Center because it is inside a hospital", 47 "fear to be without my medication", 59 "Staying apart from my loved ones", 39 "Job loss", 53 "Staying apart and isolated from other people", 42 "Fear of relating to people outside the family", 30 participants gave other answers . To question 14 "Did you find it difficult to manage the relationships with the professionals you need for your haemophilia?" the people interviewed replied: 99 (48.5%) that nothing had changed, 33 (16.2%) found no difficulty, 40 (19.6%) answered that it was difficult, 15 (7.3%) that it was very difficult and PWH would have managed it online, 17 participants (8.4%) gave other answers. To question 15 about which aspect of the current situation has had the greatest impact on their own life, the sample of people interviewed replied as follows: 22 had “difficulties related to the condition" (10.8%), 17 "difficulties related to the job (8.3%), 24 "the obligation to stay at home" (11.8%), 48 "adapting to new habits and lifestyles" (23.5%), 21 "obligation to use face masks, keep the distance and wash hands frequently" (10.4%), 26 "fear for my own and other people's health "(12.7%), for 13 it was the economic impact (6.4%), 11 replied “the restrictions when traveling” (5.4%), 16 "inability to meet the loved ones" (7.8%), 6 gave other answers (2.9%). To question 16 about whether and what kind of help the interviewee would like or need, 43 (21.1%) replied that "the support of friends or family, even if virtual", 96 (47.1%) replied that they needed more information on both Covid-19 and the Covid 19 vaccine; 58 (28.4%) reported "psychological help" both for the management of their emotional component and for the management of family relationships. 16 (7.8%) said they needed help in managing daily expenses, and wanting financial help from the government. 32 (15.7%) reported needing a greater presence of the Haemophilia Center, 13 (6.4%) by the general practitioner, and 52 (25.5%) said they did not need help. Question 17 asked whether the check-ups and the planned activities at their Haemophilia Center had been affected by the pandemic: for 82 participants (40.2%) there was no change; for 49 of them (24%) there was a reduction in all activities; 56 (27.4%) were delayed only in programmable activities such as check-ups; in 10 cases (4.9%) the pandemic caused a postponement of the switch to a new drug, while 7 gave other responses (3.5%). The last question, 18, asked if, at the date of the survey (January-April 2021), the participant had contracted Covid-19: 156 (76.4%) answered no, 24 (11.8%) answered yes, and 24 (11.8%) said they were unsure. The participants answers related to the unmet needs and perceived shortcomings are resumed in table 4. The answers to questions 13 and 16 were not shown in table 4 as they are difficult to summarize due to the high number of multiple answers

8) Were you afraid that haemo-philia could expose you to COVID-19 more?	9) Information provided by the Government, health and local authorities has… (multiple choice)	10) Did haemophilia and COVID-19 dedicated websites help you? (Multiple choice)	11) Did you need medical or psychological support? (Multiple choice)	12) The current situation may have psychological consequences in the future?	14) Did you find it difficult to manage the relation-ships with the haemophilia professionals?	15)Which aspect of the current situation has the greatest impact on your health?	17) Have the check-ups been affected by the pandem-ic?	18) Did you have COVID-19?
A little bit 93/204 (45,6%)	Confused me. 76/204 (37,2%)	No, I didn't visit any website 97/204 (47,6%)	No, I think I don't need it 115/204 (56,4%)	Yes, surely 93/204 (45,6%)	No, nothing has changed 99/204 (48,5%)	Adapting to new habits and lifestyles 48/204 (23,5 %)	No 82/204 (40,2%)	No 156/204 (76,4%)
Not at all 47/204 (23,1%)	Reassured me 42/204 (20.6%)	Yes, they made me understand more 62/204 (30,4%)	Yes, I would contact/contacted my haemophilia center 36/204 (17,7%)	Maybe yes, I don't know 66/204 (32,4%)	It's been hard: I was afraid, but I haven't had problems 40/204 (19,6%)	Fear for my own and other people's health 26/204 (12,7%)	Only on planned check-ups, but not on treatment plans and urgent visits 56/204 (27,4%)	Yes 24/204 (11,8%)
Moderately 34/204 (16,6%)	Scared me 27/204 (13,2%)	Yes, but fear and worry are still the same 23/204 (11,3%)	Yes, I would contact/contacted my family doctor 24/204 (11,8%)	I don't think so 41/204 (20,1%)	No, I didn't find difficulties 33/204 (16,2%)	The obligation to stay at home 24/208 (11,8%)	Yes, on all aspects. 49/204 (24%)	I don't know 24/204 (11,8%)
Quite a bit 22/204 (10,8%)	Made me angry, they didn't and aren't doing enough 15/204 (7,4%)	Yes, I understood and I felt reassured 8/204 (3,9%)	Yes, I would contact/contacted private professionals 6/204 (2,9%)	No, absolutely not 4/204 (1,9%)	It's been hard, I would have managed it online 15/204 (7,3%)	Difficulties related to my condition 22/204 (10,8%)	I need to switch my treatment but I couldn't 10/204 (4,9%)	
Extremely 8/204 (3,9%)	Made me feel lonely 9/204 (4,4%)	Other and multiple combined answers 14/204 (6,8%)	Yes, I would contact/contacted the psychological public service 5/204 (2,5%)		Other and multiple combined answers 17/204 (8,4%)	Obligation to use face mask, keep the distance, wash your hands frequently 21/204 (10,4 %)	Other 7/204 (3,5%)	

Table 4: Patient responses from the part of the questionnaire related to the needs and shortcomings

	Other and multiple combined answers 35/204 (17.2%)		Other and multiple combined answers 18/204 (8.7%)			Difficulties related to the job 17/204 (8,3%)		
						The impossibility of meeting the loved ones 16/204 (7,8%)		
						The economic impact 13/204 (6,4%)		
						Travel restrictions 11/204 (5,4%)		
						Other 6/204 (2,9%)		

Discussion

We are certain that our findings offer a contribution to our understanding of the psycho-logical reaction of PWH during lockdowns and subsequent phases of a pandemic by de-scribing the emotions, sensations, and level of distress experienced, as well as the impact of this on compliance with disease management requirements.

The impact of the pandemic has certainly raised concerns related to the PWH condition, manifesting more or less strongly a concern of being more exposed to the infection.

The answers show a significant need for correct information, the only thing in these cases that can indicate more suitable behaviors to face the moment. It is noted, in fact, that the information provided by the various governments, but also by the media, has not had the effect of reassuring, indeed it has often caused further confusion and a sense of uncertain-ty.

On the other hand, those who consulted the sites dedicated to the haemophilic patient, where the various federations, foundations, associations have promoted initiatives aimed at providing information about the management of the pandemic in relation to haemorrhagic diseases, were able to obtain reasons for reassurance and clarity. However, the data emerging from our enquiry reveal that almost half (47.6%) of the population interviewed, despite experiencing uncertain and insecure feelings, did not consult any site. The reasons may be various but it is certainly a fact that invites us to increase and disseminate effective and above all certified online spaces from the point of view of scientific reliability, where the haemophilic patient can get specific information for his pathology and management of social, and health situations related to the pandemic.

The results regarding the question about medical/psychological support are interesting: a high percentage (56.4%) reveals that they do not need it despite being aware that this pandemic will leave psychological repercussions (78%). Some of the patients seem to feel that correct information and good continuity in terms of communication with the teams of the HCT are already supportive and that requests for support and psychological help are more linked to a subjective management of emotions depending on the individual, and that stress related to job loss also has an impact, for those concerned.

Multiple answers were given to the question of emotions, as emotions are never unique. However, it is possible to detect emotions common to world standards and more subjective emotions linked to the social and cultural contingencies of individual local and national contexts. This indicates that some patients require more careful treatment of the emotional aspect and must always be listened to, and even more so if the patient presents fragility that can affect the quality of his life. The answers show the importance of a sup-port that is not only medical, but one which takes care of the person also from an emotional point of view, in order to create greater awareness and rationalization of their emotions; today a patient is increasingly a protagonist of his own life even in the presence of critical and uncertain events.

Regarding the patient relationship with HCT, it seems that despite the pandemic, the patient found continuity, even a strengthening of confidence. Only a small percentage were afraid to go to the Centre for fear of a possible infection and therefore preferred online management.
With regard to the management of check-ups and planned activities, a good percentage reveal continuity, and despite the fact that the check-ups were often postponed, urgent vis-its and treatment plans were always offered. However, a percentage reported inconvenience relating to difficulties in reaching the Centre and fulfilling the needs of their therapeutic plan, both for fear of contracting Covid-19 (27.9%), and for a reduction or blocking of visits to the HCT (56.3%).
But overall, the patients reported that they had no difficulty in contacting the HCT staff (64.7%), thus confirming the availability of the staff of the Centre and the adaptability of patients suffering from rare haemorrhagic diseases, that has always characterized this type of therapeutic management. It is also true, however, that by analyzing the responses of patients mainly from Asia and Africa, this percentage drops to 38.1%.

Conclusions

The survey reveals that in a condition of social isolation, it is the experience of a sense of uncertainty that prevails, which, although it is not possible to eliminate completely, can however be managed, if continuity in relationships and support is guaranteed even at a distance. This is true for all human relationships and in particular for those with chronic pathologies who find themselves experiencing a stronger sense of uncertainty. We believe that the results emerging from our work will be useful in the near future in order to im-prove professional performance in similar situations, and to optimize the synergy be-tween the HTC doctor and the patient.

References

1) https://covid19.who.int
2) Coluccia A, Marchesini E, Giuffrida AC, Rivolta GF, Ricca I, Zanon E, Luciani M, De Cristofaro R, Coppola A, Rocino A; AICE MECCOVID-19 Study Group. Addressing the impact of SARS-CoV-2 infection in persons with congenital bleeding disorders: The Italian MECCOVID-19 study. Haemophilia. 2021 Jul;27(4): e575-e578.
3) Zhang A, Liu W, Poon MC, Liu A, Luo X, Chen L, Hu Q, Yang R. Management of haemophilia patients in the COVID-19 pandemic: Experience in Wuhan and Tianjin, two differently affected cities in China. Haemophilia. 2020 Nov;26(6):1031-1037.
4) The Lancet Haematology. Bleeding disorders: adapting to change. Lancet Haematol. 2021 Jun;8(6):e383. doi: 10.1016/S2352-3026(21)00142-3.
5) Valentino LA, Skinner MW, Pipe SW. The role of telemedicine in the delivery of health care in the COVID-19 pandemic. Haemophilia. 2020 Sep;26(5):e230-e231. doi: 10.1111/hae.14044. Epub 2020 Jul 22.
6) O'Donovan M, Buckley C, Benson J, Roche S, McGowan M, Parkinson L, Byrne P, Rooney G, Bergin C, Walsh D, Bird R, McGroarty F, Fogarty H, Smyth E, Ahmed S, O'Donnell JS, Ryan K, O'Mahony B, Dougall A, O'Connell NM. Telehealth for delivery of haemophilia comprehensive care during the COVID-19 pandemic. Haemophilia. 2020 Nov;26(6):984-990. doi: 10.1111/hae.14156. Epub 2020 Sep 30. PMID: 32997849; PMCID: PMC7537516.
7) Dorgalaleh A, Tabibian S, Baghaipour MR, Dabbagh A, Bahoush G, Jazebi M, Bahraini M, Fazeli A, Yousefi F. Challenges and concerns of patients with congenital bleeding disorders affected by coronavirus disease 2019. Blood Coagul Fibrinolysis. 2021 Apr 1;32(3):200-203

Funding

This research received no external funding

Conflicts of Interest

The authors declare no conflict of interest.

Corresponding author

Dr. Gianluca Sottilotta. UOSD Microcitemie - Emostasi e Trombosi. Grande Ospedale Metropolitano di Reggio Calabria (Italy). E-mail: gianluca.sottilotta@virgilio.it

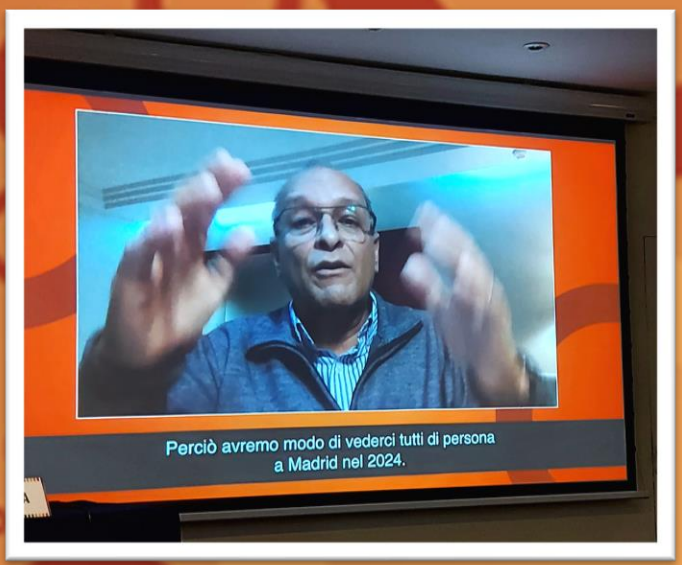
8° CONVEGNO INTERREGIONALE

NUOVE SFIDE NELLA GESTIONE DELLE MALATTIE EMORRAGICHE CONGENITE ED ACQUISITE: DALLE NUOVE TERAPIE ALLE COMPLICANZE TROMBOTICHE

CATANIA 3 DICEMBRE 2022


A. TRIPODI
8 CONVEGNO INTERREGIONALE
CATANIA 3 DICEMBRE 2022


P.M. MANNUCCI
8 CONVEGNO INTERREGIONALE
CATANIA 3 DICEMBRE 2022


Perciò avremo modo di vederci tutti di persona
a Madrid nel 2024.


E. ZANON
8 CONVEGNO INTERREGIONALE
CATANIA 3 DICEMBRE 2022


M. NAPOLITANO
8 CONVEGNO INTERREGIONALE


NVEGNO
RREGIONALE
IA 3 DICEMBRE 2022


M. MORFINI


O. DI GREGORIO