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ORIGINAL ARTICLE

Evolution of Hemophilia Care in India

Kanjaksha Ghosh[1]

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Abstract Haemophilia is a high cost low volume disease. Being a relatively uncommon condition governments of the day are not very interested in developing comprehensive care for such a condition. Patient's society where such kind of patients come together under one umbrella and fight for their rights and proper management of the condition has important role to play in developing and helping to deliver high standards care in such a condition. Haemophilia Federation of India, a patient's organization played a stellar role in developing haemophilia care in this country and continues to do so today, present article explains how this organization engaged itself through local, national and international interaction in evolving haemophilia care in this country. The present description can act as a template for developing similar architecture of care for rare but difficult and costly to treat disorders'.

Keywords Haemophilia · Haemophilia federation of India · Government · Gene therapy · Recent advances in treatment

Introduction

Doctors in India or at least in certain centers in India were quite aware of hemophilia and some of the major bleeding disorders from early 1960's. They have published research papers, laboratory, investigations, and highlighted certain complications of the disease from that time [1–4]. However in the area of management of a person with hemophilia (PWH) very little was available except whole blood and Fresh Frozen plasma (FFP). Cryoprecipitate production by the blood banks of this country was standardized only in 1980's [5, 6] and even today many of the blood banks in the country do not produce cryoprecipitate and other blood components regularly. It may not be out of place to document here that Dr Judith Pool described how easily cryoprecipitate can be produced in a standard blood bank from FFP, using very simple devices way back in 1964.

Diagnostic facilities for hemophilia were available only at Kolkata, Delhi, Mumbai, Vellore, Varanasi and Chandigarh. Hemophilia Federation of India (HFI) was established in New Delhi as a patient Organization in 1983, it started with less than 12 families of PWH (Person with haemophilia) as founding members. The Challenges faced by PWH in initial years and the fight by HFI and its associated chapters have been described in our previous review [7]. However there has been spectacular progress in the delivery of care for PWH in India through good cooperation of HFI with state governments, state health authorities, central (federal) government of the Country and the World Federation of hemophilia. The present account provides a brief description of progress in various areas of haemophilia care over the years.

I. Development of Chapters of HFI and Spread of Hemophilia Care Centers Across the Country

Following constitution of HFI, a patient organization for haemophilia management and care in New Delhi, the capital of India, the main challenges of the office bearers of HFI was: (i) How to spread its activity and execute plan of action across this vast country. (ii) How the care of the

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✉ Kanjaksha Ghosh
kanjakshaghosh@hotmail.com

[1] Surat Raktadan Kendra & Research Centre, Surat, Gujrat, India

PWH could be delivered in more than 30 of the populous states in this country where a large majority of the states have population greater than France or Germany and health care infrastructure is not optimum for hemophilia care. Initially a few chapters i.e. Kolkata (where hemophilia and thalassemia care was already combined in the form of a blood bank operation with packed RBC for thalassemia patients and FFP/cryoprecipitate for hemophilia patients), was already in existence along with a blood bank for the society and in Trivandrum where a society of PWH was in existence before HFI was formed, along with Delhi and Madras (Chennai) took the lead.

Factor concentrates, the main product recommended for treatment of haemophilia patients were not available anywhere in the country and in mid 80's, a company producing freeze dried cryoprecipitate had to be closed down because several patients receiving both cryoprecipitate and other plasma based products (anti Rh immunoglobulin) developed HIV seropositivity [6]. More over government hospital were not adequately sensitized for the management and diagnosis of haemophilia. Hence (New) Delhi Chapter developed hemophilia care centers at Lions Club Hospital, a private hospital, Kolkata already had it chapter's care centers at its own premises and In Ramkrishna Seva Pratisthan, a charitable hospital and Madras developed their care facility in voluntary Health society hospital, another charitable organization and Trivandrum chapter's care remained linked to a private nursing home.

One of the major challenges in early years was that there were very few doctors who knew how to provide care to haemophilics, particularly when treatment products were limited and demands for such products were high. Only 3 or 4 laboratories across the whole country were capable of doing clotting factor assays and almost none were in a position to perform inhibitor assay.

Hence in the first few years of existence, HFI tried to bring international expertise in this country. Famous international haemophilia experts like Prof. P Mannucci, Prof. Christine Lee, Dr. Louis Alederot, Dr. Martinovitch, Dr. Alessandro Gringeri trained a group of doctors from different parts of India on how to care for PWH. They also examined many PWH and provided necessary management instructions. Many more foreign experts paid regular visits to this country, conducted regular patient camps and trained our clinicians, physiotherapists, pathologists and surgeons.

Mr. Angus Mc-craw made several visits to various institutions to train laboratory skills for coagulation work. World Federation of Haemophilia (WFH) provided several twinning opportunities and Individual Fellowships for training in hemophilia care from advanced centers in the world and recognized two important centers in India i.e. CMC. Vellore and National Institute of Immunohaematology and Hematology unit of KEM Hospital at Mumbai as two International Hemophilia Training Centers (IHTC).

These two IHTCs have trained many doctors, physical therapists and laboratory personnel across India and from many developing Countries, IHTC Mumbai has even motivated research publication from one if its trainees from Nepal [8, 9].

Between 1983 and 1994 i.e. in its more than 10 years of existence of HFI, less than 15 chapters were created across the country and a grand plan was needed to develop a hierarchy of management of the organization with each chapter office bearer with some management skills. A substantial financial grant from Danish government in association with Danish Hemophilia Society (DANIDA project) working in India in association with HFI from 1998 to 2005 made that possible. This association and training by hand holding lead the foundation of present structure and functional attributes of HFI.

Mr. Terkel Anderson and several of his colleagues from Danish Hemophilia Society took the pains to oversee gradual transformation of the HFI. HFI laid the foundation of additional 10 chapters through DANIDA project. Considering India is a big country, 4 regional offices of HFI were established to oversee the functioning of the local chapters. A regional manager was appointed with an office to manage the development and function of the chapters and coordinating chapter activities in the region. It was understood that without substantial financial back up an organization like HFI will not survive. Unlike many other NGO's in the country HFI even today does not receive any fund from the Government of India. Today more than 90 chapters of HFI are working in the country. Along with help of state governments and central government the society plans to indentify, open and run more than 200 hemophilia treatment centers in near future.

Majority of these centers are now located in government hospital and quite a few is also run by charitable organizations or private entities. Till 2003 factor concentrates was provided by the HFI to PWH in the country as the state or central government was reluctant to take care of PWH except in some cosmetic way i.e. Cryoprecipitate were made free for PWH in the state of Maharashtra and in few more states, PWH were given identity Cards etc. Factor concentrates were costly and number of PWH requesting treatment were increasing exponentially each year from 12 in 1983, 200 in 1988, 2000 in 1998, 5000 in 2000, and 21,000 today in 2018.

Initially HFI relied on factor concentrates gifted by various international organizations and also factor concentrate firms. Most of these concentrate were very near expiry date. However these near expiry date factor concentrates were quite active in stalling bleeding in PWH but due to various reasons mainly financial the PWH of this country continued to use near expiry clotting factors.

HFI also had to face criminal charges in a court of law for storing nearly expired factor concentrates, a large amount of which was also eventually destroyed by the licensing authority.

II. Engaging the Highest Courts of Indian States Through Public Interest Litigation

It became apparent by early 2000 that it is not possible for a charitable organization like HFI to adequately supply factor concentrates of good quality, free of lost or with minimal cost to PWH without government support. However state governments were not willing to take hemophilia care burden whole heartedly into their health programmes. Mr. Brian–O Mahoney, the then president of World Federation of hemophilia tried to engage central government for hemophilia care in India through his well planned advocacy programme. However his visit and the programme itself had minor influence on the government's desire to help the PWH in this country.

Meanwhile hemophilia community in India also felt unhappy because one of the biggest WFH programme "Global Alliance for Progress" or GAP [10] which was supposed to help developing Country to develop its hemophilia care left no foot print in a large developing country like India.

While WFH had several argument, why India cannot be selected for the programme, one of the strongest argument was that, health care in India is state's responsibility, but not federal responsibility, this arguments was not convincing enough.

After long deliberations and review as to how the courts in India have forced both State and Central (feudal) government to take affirmative action in environmental pollution and health care, HFI took the decision to go to each of the State's highest courts (High Courts) with a public interest litigation as to why haemophilia care should not be the government's responsibility and be a part of their health care programmes.

Starting with New Delhi, Uttar Pradesh, state after state received pronouncement of their highest courts favouring the HFI's contention and state governments grudgingly agreed to take up haemophilia care as one of their health programmes. Some state like Pondicherry, Tamil Nadu, and Karnataka etc. readily agreed to do so without courts' intervention. However few states were still out there not to agree on to shoulder hemophilia care. Eventually all of them finally understood the reason and agreed to take medical care of PWH.

These were the biggest victories of the PWH movement in India. However this was not achieved without extremely hard work by HFI and its chapters, because Court's in the country wanted data on number PWH in different parts of this Country along with their health status. This data was not available in a concrete fashion anywhere with the state or with central government.

Hence the need for developing a National Haemophilia registry was acutely felt and the time was ripe because the developing chapters (from 40 in 2004 to 90 in 2018) already compiled the names and addresses of PWH in their respective areas in the country.

III. Development of a Haemophilia Registry at the National Level

Though at every chapter level there was a list of PWH in this country, the list was not maintained meticulously, hence whenever the organization used to approach a state government for help the standard reply was there are few PWH in the state and it is not a medical challenge at all. At this point need for a nationwide hemophilia registry was felt. The programme was initiated in 2009–2010 and with funding from a corporate under the aegis of HFI at St. John's Medical College, Bangalore.

One of our PWH member and his team who had extensive expertise in software development helped us to put up the registry with minimal cost and though as yet it is not a dynamic registry and has pitfalls of chapter wise list of PWH with many duplications. Progressive corrections of the list of PWH are made constantly. By 2018 with 21,000+ entries this registry became one of the largest haemophilia registries in the World and several research papers came out from the data compiled in the registry [11, 12]. This registry is now helping HFI to direct help where it is needed, to put up advocacy programme to state governments and helping HFI in raising funds through corporate social responsibility.

Now time has come for government of India to totally fund this registry. National health mission as well as ICMR is already planning to help in this area. This registry also registers other bleeding disorders and an account of rare bleeding disorders in India did originate in part from the registry data [11].

The registry is not yet complete or dynamic but with more than 21,000 PWH the Indian Haemophilia registry hold 3nd place in the world after USA and Brazil on the number of PWH identified and treated in any country.

IV. Interaction of Central (Federal) and State Governments with Haemophilia Federation of India and Its Chapters for Improving Care in India

Care of PWH is likely to improve significantly if central government of India also could step into help the state governments and with that idea HFI engaged central government from the beginning of 12th 5 year plan.

Even before this attempt, the Central Government through its ministry of railways did provide free and heavily subsidized railway tickets for PWH and one of his attendants respectively. In addition made cryoprecipitate and plasma therapy free for PWH for last several years beginning from 2001 through National Aids Control Organisation (NACO) initiative.

This year central government declared severe haemophilia along with thalassemia major and sickle cell disease to be a bench monk disability qualifying them for reservation in Jobs and education. Central government also agreed to fund state government for haemophilia care though a funding mechanism via National Health mission and agreed to set up coagulation laboratories across country to help early diagnosis of haemophilia. Other benefits of having coagulation laboratories spread evenly across the country outside mere haemophilia care was also impressed on policy makers leading to this change.

V. State Governments and Haemophilia Care

Many state governments of India was reluctant to spend large amounts of money for managing health care in patients with chronic disabilities. Even their record on preventive and primary health care is not bright. Hence for haemophilia care there was and is still a great deal of reluctance to spend money for a condition which has already been described as high cost low volume chronic disorder. However haemophilia movement in all dimension forced many of the state health authorities to develop some care for their PWH. These development are (1) Cases fought against the state at high courts for not doing enough for haemophilia care for their citizen. (2) Activism of haemophilia federation of India's local chapters to continue advocacy programmes in various states. (3) Haemophilia federation of India mobilizing many likeminded influential personalities to induce Central governments to do some that for haemophilia Care. (Hence the help to the State governments though National Health Mission.)

VI. Exclusive Advocacy Programme Conducted by Hemophilia Federation of India, State Chapters and Ably Associated by World Federation of Hemophilia

As a result of all these combined activities and verdicts from high Courts of different States asking State governments to tell Judges concrete programme for haemophilia care. This resulted in slightly different application of the programme in different states. In framing these programmers the haemophilia registry data provided substantial help as state wise already diagnosed patient's details were available in the registry. Some state government generously provided funds to the health care infrastructure available in that State (cf. Tamil Nadu).

However majority of the states selected a few medical colleges and/or civil hospitals through which the treatment products were provided. Few states preferred to drag their feet and still PWH in those states were mainly received unsafe wet plasma based therapy. Finally with commitment of fund from national health mission all states have for last 2 years started providing free factor concentrates to PWH.

VII. Deeper Engagement of World Federation of Haemophilia for Haemophilia Care in the Country

For many years till 5–6 years back, help from World Federation of Haemophilia was restricted to (1) giving few international fellowships for haemophilia management every year (1–2 persons), (2) Helping to twine one developed Western Country haemophilia centre to one treatment centre or chapter in the country (3) Recognizing 2 International haemophilia training Centers i.e. one at CMC Vellore and another at National Institute of Immunohaematology and KEM Hospital in Mumbai.

In addition WFH used to provide some technical inputs in terms of Advocacy programme and later on some small financial grant (Rs 25–30 lakhs/year) to carry on with the advocacy programme.

The important Contribution to develop HFI's hierarchical infrastructure and volunteer training through DANIDA project has already been mentioned. DANIDA project was also realized through WFH help.

However since last 5–6 years there has been a much deeper engagement of WFH with HFI and the successive presidents of WFH met Central health ministers to impress upon the need for governments involvement in haemophilia care in the country.

WFH from Biogen Idec company received a huge quantity of long acting factor eight and factor IX as humanitarian donation and a substantial amount of that (@ > 50 million units/year) is now reaching to our PWH through HFI and its various chapters.

VIII. Role of Haemophilia Federation of India in Developing Prenatal Diagnosis and Carrier Detection Facility is in India

HFI played an important role in shaping the development of prenatal diagnosis and carrier diagnosis facilities in two international Haemophilia Training Centers in India and subsequently through their advocacy programmes in several centers of excellence in this country. These services as it developed along with many other services for haemophilia care provided a perfect example of how patient organization can develop close relationships between academic centers, doctors and local governments to develop services for their care and this model is capable of duplication for many other diseases. Presently every year approximately 100–150 family is undergo carrier detection test and same number of families are also counseled and tested for prenatal diagnosis. As this test is costly for poor patients, HFI and even chapters provide financial help to poor families. HFI raised some funds in this area via corporate social responsibility route too.

IX. Nationwide Inhibitor Detection Programme

One of the important complications of haemophilia particularly for haemophilia A is development of inhibitor to factor VIII. This complication increases the cost of care several folds as factor VIII concentrates becomes increasingly ineffective with rise in inhibitor levels. The products needed for treating patients with inhibitor are extremely costly. Moreover inhibitor assay and quantification is technically exacting and time consuming and costly. Hence there was a need to assess the inhibitor frequency against both factor VIII and factor IX in Indian PWH. Fortunately a corporate body agreed to fund the exercise and they developed a good logistics of plasma transfer to an IHTC maintaining the cold chain. Over the years more than 7000 PWH were randomly tested (33% of total diagnosed PWH population in India) for inhibitor. Around 5% of total severe and moderately severe haemophilia A developed inhibitor in our country with higher prevalence in certain south Indian states. A partial report of this study has already been published [13].

X. Future of Haemophilia Management and Research in India, Continuing Role of Haemophilia Federation of India

Today Haemophilia Federation of India can boast of one of the world's largest haemophilia registry with more than 21,000 such patients. At one end it should be the role of the patient's society to get all the severely and moderately affected haemophilia patients in the register.

It is felt that we have not yet identified more than 20% of the likely severe and moderately severe haemophilia patients from our country. Hence we need more wide spread diagnostic facilities and at least all the medical colleges and 750 district hospitals in the country should have this facility without any further delay.

Already interaction of HFI with National Health mission resulted in fateful decision to setup coagulation laboratories at all the districts of this country. This will not only help haemophilia patient's investigation but will help innumerable cases of acquired and other undiagnosed of bleeding disorders.

Many of our haemophilia patients are affected by transfusion transmissible hepatitis with hepatitis C leading the list. They need to be treated with modern drugs which are very effective but costly. It is heartening to learn that national health mission may well agree for free medicine for this condition.

One of the major challenges for proper haemophilia care in this country is the lack adequate expert manpower i.e. hematologists, pathologists, physiotherapists, orthopedic surgeons, dentists who know how to manage a patient with hemophilia in their specialized fields. There are no training programme in this country, available for haemophilia nurse, a pivotal position for haemophilia care.

HFI and all its chapters regularly organize various CME to educate the relevant man power. In addition IHTCs and different renowned medical colleges conduct regular training/workshops to create manpower for haemophilia management in this country.

Finally standards of haemophilia care across the world is through primary prophylaxis and eventually gene therapy. In India both government and HFI has to take the lead in this area. Fortunately few centres have already started low and intermediate dose prophylaxis as well as immunomodulation therapy for inhibitors. These are encouraging signs for the PWH population. Though with provision of adequate factor concentrates the proper management of haemophilia patients should shift from episodic therapy to home therapy to regular prophylaxis or replacement therapy. However for a country like India this may not be easily achieved and HFI will need to continue its struggle with health establishments of the country to do so. As newer therapy and newer mode of administration of these therapies for haemophilia care and for care of its complications become available [14] they need to be integrated into future haemophilia care. Being costlier they may not be accepted by the governments of the day. Moreover HFI needs to keep a keen eye on complications with various new therapies (e.g. Thrombosis with certain new products) and need to advice the government as to which of the products are likely to be beneficial for them.

Long acting factor concentrates [14, 15] and gene therapy [14–16] and newer forms of Immunomodulation in cases with Inhibitor [17, 18] are likely to become the dominant points of discussion on haemophilia care in future. Physical therapy is a very important component of haemophilia care and though HFI has been trying its best to implement this modality of therapy across the country, there is some reluctance to adopt this in a whole hearted manner as there is belief across the treaters and those who are going to be treated that once adequate factor concentrates are available other ancillaries of haemophilia care will not be required. This misconception needs to be challenged at every level.

As we overcome our initial challenges of haemophilia care newer challenges i.e. chronic liver disease, obesity, other lifestyle oriented and degenerative diseases will affect PWH population as they become older. HFI will then have a very different role to play to keep its member s healthy in body, mind and spirit [19].

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Compliance with Ethical Standards

Conflict of interest Author declares no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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