Abstract

A survey was performed in late-2003 by questionnaire to all paediatric and adolescent departments under the Hospital Authority of Hong Kong to study the epidemiology and clinical status of local haemophilia patients under 19 years of age. A total of 90 patients were recruited, corresponding to a local prevalence of 6.4 per 100,000. Among these 90 patients, 83.3% were haemophilia A and 16.7% were haemophilia B cases. Maternal carrier status was uncertain in 44.6% of patients and genotypic assessment was not performed in most of these cases. None had received primary prophylaxis although 42.9% of them were severe haemophiliacs and 46.4% had already suffered from chronic arthropathy. Inhibitors were detected only in 8.1% of patients. None was infected with human immunodeficiency virus but hepatitis C antibody was detected in 12 and hepatitis B surface antigen was positive in two patients. All but one of the infected patients were older than 13 years with only one patient suffering from chronic hepatitis. Twelve patients had history of intra-cranial haemorrhage. While infective complications were uncommon in our young haemophilia patients, improvement in carrier detection, prevention and treatment of haemophilic arthropathy should be considered in the future development of local haemophilia care.

Key words

Children and adolescents; Haemophilia; Epidemiology; Clinical status
Introduction

Haemophilia is an inheritable, congenital and life-long disease without a cure at the moment. Affected individuals are vulnerable to recurrent bleeding episodes which are painful, disabling and potentially life threatening. Lives of haemophilia patients have traditionally been visualised as overwhelmed by multiple serious complications and crippling disabilities that will not only cause relentless physical and psychological sufferings but also deprive them of the abilities to contribute to the society. Fortunately, remarkable progress in haemophilia care has been achieved through the past few decades. The introduction of factor concentrates with increasing level of safety, the spreading practice of prophylactic factor replacement, the development of effective intervention of chronic arthropathy, the improvement in management of human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infections as well as the advances in carrier detection and prenatal diagnosis have all contributed to redefine the once gloomy fate of haemophilia patients. With adequate financial support and cooperation from expertise of various fields, comprehensive management of haemophilia nowadays should include treatment and prevention of the primary disease and its complications with a view to strive for a normal and functional livelihood for the affected and to avoid unplanned or unexpected birth of haemophilia babies. The current review was conducted to study the epidemiology, clinical status and practice in the management of paediatric and adolescent haemophilia patients in Hong Kong with the aim to identify areas for improvement in the local care of this group of patients.

Method

Our study was performed by sending questionnaires to all paediatric departments of public hospitals under the Hospital Authority (HA) in late-2003 asking for epidemiological and clinical information on all haemophilia A or B patients they have ever managed, including those who have died, lost to follow up or been transferred to other departments. Information enquired included patients' demographic data; severity and type of haemophilia; maternal carrier status; use of prophylactic factor replacement; development of inhibitor, HBV, HCV or HIV infection and any other significant complications. Definitions of clinical status were specified in the questionnaire whenever possible to allow more meaningful analysis of responses from different hospitals (Table 1). A descriptive analysis of data was performed using SPSS 11.0 computer software.

Table 1 Definition of clinical status

<table>
<thead>
<tr>
<th>Severity of haemophilia</th>
<th>Baseline Factor VIII/IX level &lt;1% = severe; 1-5% = moderate; &gt;5% = mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier status of mother</td>
<td>Classified as carrier, non-carrier or uncertain at the discretion of reporting paediatrician</td>
</tr>
<tr>
<td>Primary prophylaxis</td>
<td>Long term prophylactic factor replacement started prior to the onset of joint damage (presumptively defined as having had no more than one joint bleed)2</td>
</tr>
<tr>
<td>Secondary prophylaxis</td>
<td>Long term prophylactic factor replacement started after multiple joint bleeds2</td>
</tr>
<tr>
<td>Inhibitor</td>
<td>High responder = brisk anaemnesis upon factor re-exposure with peak historical inhibitor titre ≥5BU3</td>
</tr>
<tr>
<td></td>
<td>Low responder = lack of anaemnesis upon factor re-exposure with peak historical inhibitor titre &lt;5BU3</td>
</tr>
<tr>
<td>Chronic haemophilic arthropathy</td>
<td>Presence in any joint of radiological evidence of haemophilic arthropathy, chronic pain, deformity, limitation in range of movement or restriction in normal function even in the absence of haemarthrosis</td>
</tr>
<tr>
<td>Chronic hepatitis / cirrhosis</td>
<td>Defined at the discretion of reporting paediatrician</td>
</tr>
<tr>
<td>Other complications</td>
<td>Intracranial haemorrhage, haemophilic pseudotumour, Volkman's contractive, transmission of infections agents other than HBV, HCV or HIV, and any other complications that were considered significant by the reporting paediatrician</td>
</tr>
</tbody>
</table>
Results

Amongst all the 13 HA paediatric departments, 9 have ever managed haemophilia patients. One of these 9 departments, where 1-2 haemophilia patients have ever been managed, did not respond to the questionnaire. All the remaining 8 departments responded by providing relevant information on all their haemophilia patients. Only the data of those younger than 19 years of age when this study was performed were presented as follows.

Altogether, 89 male and 1 female patients aged 0.4 to 18.9 (mean = 11.8, median = 12.5) years were reported. They included 75 (83.3%) haemophilia A and 15 (16.7%) haemophilia B cases (Figure 1). One patient had been lost to follow up since 11.5 years old and none had died. Baseline factor levels were reported in 84 (93.3%) of patients among whom 17 (20.2%) were mild, 31 (36.9%) were moderate and 36 (42.9%) were severe haemophiliacs (Figure 2).

In 83 (92.2%) patients, carrier status of their mothers were specified. Thirty one (37.3%) mothers were classified as carrier, about 90% of whom have a positive family history of haemophilia other than the index patients and genotypic analysis was performed to establish the carrier status in 3 cases. Fifteen (18.1%) mothers were classified as non-carrier but the carrier detection method was specified only in 4 cases including coagulation study in 3 and genotypic assessment in 1. For the 37 (44.6%) mothers who were classified as having uncertain carrier status, the carrier detection method was not specified and genotypic assessment was not performed in the majority of cases (verbal communication with reporting paediatricians).

None of the 90 patients has received primary prophylactic factor replacement though secondary prophylaxis has been given to 33 (36.7%) patients. Inhibitor status was specified in 86 (95.6%) patients with 7 (8.1%) being positive. This included 5 haemophilia A low responders, 1 haemophilia A high responder and 1 haemophilia B high responder. Of 84 (93.3%) patients with joint status reported, 39 (46.4%) had chronic arthropathy with 5 having limitation in daily activities, 2 requiring walking aids and 1 being bed ridden.

Data on hepatitis and HIV infection were reported in 81 (90%) patients (HIV antibody positivity = 0, HBsAg positivity = 2, HCV antibody positivity = 12). All HCV antibody positive patients were ≥13 years old when this study was performed. One patient, who was HBsAg and HCV antibody positive, had chronic hepatitis but none had cirrhosis or liver cancer. Other complications were reported in a number of patients including intracranial haemorrhage (ICH) in 12, intra-abdominal haematoma requiring operation in 2, iliopsoas muscle bleeding with femoral nerve compression in 2, haemothorax in 1, haemophilic pseudotumour involving the calcaneum in 1.

Discussions

Care for haemophilia patients is costly with a significant proportion of expenditure being spent on factor concentrates. As these essential medications are provided without the need for extra payment in addition to the usual in-patient or out-patient charges in local public hospitals, it would be reasonable to assume that most haemophilia patients in Hong Kong will be under the care of HA. Taking the total number of haemophilia patients <19 years of age

![Figure 1](image1.png) Age distribution of patients.

![Figure 2](image2.png) Baseline factor level of patients.
to be 90 as reported from all HA paediatric departments in our study, the prevalence of haemophilia in the 1.4 million local paediatric and adolescent population (Demographic Section, Census and Statistic Department, HKSAR – personal communication) was estimated to be 6.4 per 100,000 with a similar distribution of haemophilia A (83.3%) and B (16.7%) cases as compared with Western figures.5

Carrier detection is considered a very important element in haemophilia care for the purpose of genetic counseling, family planning, disease prevention and perhaps also reducing the risk of birth related intracranial haemorrhage in unexpected haemophilia babies of unsuspected carriers.5-7 When there is a positive family history of haemophilia in the maternal side other than the index patient, obligatory carriership may be established simply by a pedigree analysis. However, in the much more common scenario of an isolated case of haemophilia in the family, laboratory investigations will be necessary for clarification of carrier status. The commonly employed APTT screening, assay of factor VIII, IX and factor VIII:C to vWF ratio are unreliable for the purpose due to considerable overlap between the ranges of normal and carrier factor levels, effects of Lyonization, ABO blood group, age and OC pills on the test results.5,6 A mathematical model of discriminant analysis that takes into account of all the above factors in addition to pedigree data has been designed for a more precise prediction of the probability of carriership.5,8 Nevertheless, the model is complicated and difficult to be applied practically.

On the other hand, advances in the technique of genetic diagnosis for haemophilia nowadays have allowed a very high rate of accurate carrier detection, achievable not only in the developed Western world but also in some of our neighbour South East Asian countries and even in the developing Indian peninsula.6,9 In Singapore General Hospital, for instance, by adopting a strategy of intron 1 and 22 inversion mutations screening followed by linkage studies of polymorphisms using intragenic and extragenic markers, carrier status can be clarified in 96% of women from haemophilia A families.10 With a similar approach using both linkage studies and direct mutation detection by a novel multiplex polymerase chain reaction – conformation sensitive gel electrophoresis, an 100% rate of carrier detection and prenatal diagnosis in families with haemophilia A and B can be achieved in a cost-effective way affordable even in India.11 In Hong Kong, we have similarly good molecular tools and free service for the prenatal diagnosis of haemophiliac fetus with positive family history. However, such service is not routinely available for children or non-pregnant adult carrier detection.

As reported in the literature, the probability for a mother of an isolated case of haemophilia in the family to be a carrier has been estimated to be about 0.85.6 With reference to this estimated probability of carriership, the proportion (37.3%) of our patients with established maternal carriership is rather low. In addition, in almost half (44.6%) of the patients, maternal carrier status has been classified as uncertain and yet genotypic assessment has not been performed. In line with the concept of comprehensive haemophilia care, there appears room for improvement in haemophilia carrier detection in Hong Kong.

Haemarthrosis is the commonest type of bleeding in haemophilia. Blood inside the joint can cause inflammation, hypertrophy and increased vascularisation of the synovium as well as damage to the articular cartilage. With an increased tendency to bleed as a result of the above changes, the diseased joint will eventually end up in a state of severe haemophilic arthropathy through a vicious cycle of bleeding and joint damage.12,13 Theoretically, by giving factor replacement prophylactically to prevent rather than to control haemarthrosis, vicious cycle of joint destruction may be attenuated or even be avoided altogether if effective prophylaxis is commenced early in life before any significant joint damage.

Numerous observational and case controlled studies, some of which being large scale international multi-centered long term cohort studies, have demonstrated that severe haemophilia patients can enjoy reduced frequency of haemarthrosis and other significant bleeding problems as well as better orthopaedic outcomes and quality of life when put on prophylaxis.14-18 Long term prophylaxis commenced within 2 years of age or after the first episode of haemarthrosis and before the development of any joint damage (primary prophylaxis) has allowed severe haemophilic patients to have joints that are entirely normal or only very mildly affected by haemophilic arthropathy when they become adolescents.14 For those who have prophylaxis started at an older age after multiple joint bleeds (secondary prophylaxis), certain degree of established joint damage is often inevitable. Even though their frequency of haemarthrosis could be decreased and clinical orthopaedic status improved with prophylaxis, their arthropathy continue to progress radiologically.14,19

While the amount of factor usage and hence the cost of standard intensive regimen of primary prophylaxis is much higher than that of on demand treatment; an individualised,
response-guided low dose prophylaxis regimen, has been shown to be equally effective but associated with less factor consumption and thus a significant cost reduction.\textsuperscript{20,21} In addition, haemophilia patients brought up with early prophylaxis require decreasing factor replacement with age probably because of a well preserved orthopaedic status in addition to an improving sense of trauma prevention and an increased in half-life of infused factor with age.\textsuperscript{20,22} On the contrary, factor requirement in those patients receiving on demand treatment tends to escalate with age as a result of increasing frequency of haemarthrosis and joint pain due to worsening arthropathy.\textsuperscript{23} The factor consumption of these 2 groups of patients has actually been shown to be comparable when they reach adulthood.\textsuperscript{24} Although continual vigilance is required on the transmission of pathogens through the use of factor concentrates, the safety record of current plasma derived and recombinant factor concentrates are excellent and there has been no report of an increase in incidence of inhibitor formation with the wide adoption of prophylaxis.\textsuperscript{2,25}

Prophylaxis is generally accepted nowadays as the ideal treatment for severe haemophilia patients. Many national and international authorities, including World Health Organization (WHO), World Federation of Haemophilia (WFH), United States National Haemophilia Foundation and Canadian Haemophilia Society have recommended primary prophylaxis as the optimal treatment for severe haemophilia A and B patients.\textsuperscript{26-29} A multinational survey in 16 European countries has also revealed that in >90% of treatment centres, strict primary prophylaxis or long term prophylaxis after >2 episodes of haemarthrosis is recommended for all severe haemophilia patients.\textsuperscript{30}

As at the time of our study, primary prophylaxis was not given to any of our patients despite the fact that 42.9% of them were severe haemophiliacs. Without primary prophylaxis, chronic arthropathy occurred in 46.4% of our patients, 9.6% had functional disabilities ranging from limitations in daily activities to a bed ridden state and 36.7% subsequently required secondary prophylaxis. Such a significant magnitude of chronic arthropathy in our patient cohort calls for serious consideration for a change in the local practice by adopting primary prophylaxis to severe haemophilia patients in conformation to the prevailing recommendations world wide. This can benefit the few currently very young and orthopaedically intact patients as well as our new haemophilia patients in the future. In addition, it also highlights the need to look into the local availability of interventions for haemophilic arthropathy like radioisotope or chemical synoviorhesis, arthroscopic or open surgical synovectomy and a whole spectrum of orthopaedic surgeries ranging from joint debridement to arthroplasty.\textsuperscript{31-35} Radioisotope synoviorhesis, a technique of inducing synovial fibrosis by intra-articular injection of radioisotopes, is particularly worth exploring. Having been practiced for over 30 years in thousands of patients down to 5-6 years of age with excellent safety record in regard to induction of malignancy and damage to epiphysis, this economic and minimally invasive technique has been shown to be very effective in reducing pain and bleeding as well as improving the mobility of joints at the early stages of haemophilic arthropathy.\textsuperscript{36,37} In well selected cases, good to excellent effect which can last for many years are to be expected after the procedure.\textsuperscript{32,38} This will not only improve the functional capacity and quality of life of patients but also contribute to the reduction in the use of factor replacement.

With meticulous attention to the selection of "safe" blood donor and improvement in the method for viral attenuation in the manufacturing process, the risk for infection through the use of plasma derived factor concentrates, has been considered negligible for HIV and very low for HBV and HCV ever since early 1990s.\textsuperscript{26,39} An even higher level of viral safety is to be expected for the newer recombinant products.\textsuperscript{40,41} Like other developed countries, complication of hepatitis B or C was uncommon and HIV infection was rare (0 case in our cohort) in our young haemophiliacs. All our 12 HCV antibody positive and 1 of the 2 HBsAg positive patients were ≥13 years old. The relatively benign course of HCV infection in children as reported in the literature was substantiated by the fact that only 1 of our hepatitis virus-infected patients, who was simultaneously infected by HBV and HCV, has developed chronic liver disease. Nevertheless, given the availability of effective combination treatment for chronic hepatitis C using interferon and ribavirin whereby an overall sustained remission rate of around 50% is to be expected, HCV antibody positive patients should be regularly monitored and treatment considered when chronic hepatitis develops.\textsuperscript{32,45}

Intracranial haemorrhage is the commonest cause of death from bleeding in haemophilia which can develop after a trivial or even no recallable head injury in about half of the cases.\textsuperscript{44} Significant association exists between a delay of factor replacement (> 6 hours from head injury) and the development of ICH.\textsuperscript{45} Our finding of a history of intracranial haemorrhage in 13.3% of patients calls for vigilance to this potentially lethal bleeding event. Perhaps, a policy of early liberal use of factor replacement will be advisable in case of any suspicion of a recent head injury,
however minor it may be.

A major drawback of this voluntary multi-centred, retrospective questionnaire survey is the incompleteness of reported data. Nevertheless, the data was completely missed only in 1 to 2 patients from 1 non-responding hospital. For the 90 studied patients, response to each study question was obtained in ≥90% of cases. With such a limited degree of missing data, we believed that our study has served to reveal the current clinical and epidemiological picture of our local paediatric and adolescent haemophilia patients without significant distortions. Two major areas for improvement in the care of this group of patients, namely, haemophilia carrier detection as well as prevention and treatment of haemophilic arthropathy were identified. Improvement in the availability of genetic diagnostic techniques in carrier detection, adoption of primary prophylaxis to severe haemophilia patients and consolidation or development of interventions for haemophilic arthropathy should be important issues to be considered in the future development of haemophilia care in Hong Kong.

References