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THE CHALLENGE OF AN AGEING HEMOPHILIC POPULATION

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REVIEW ARTICLE

The challenge of an ageing hemophilic population

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Introduction

The world population is ageing in an unprecedented way, in part as a result of a major increase in life expectancy through decreased infant mortality and improvements in healthcare, housing and diet. Globally, the number of older persons is expected to exceed the number of children by 2047, but in developed countries this milestone was passed in 1998. [1] An ageing population is likely to have wide-ranging consequences for the economic and social environment of society and as older individuals have more chronic illness, the impact of a larger population of elderly individuals will be significant for healthcare systems. [1,2]

The world population of persons with hemophilia (pwh) is also likely to have benefited from the general factors contributing to health improvement, but have also benefited more specifically from advances in hemophilia care such as the availability of safe, effective factor concentrate, the development of comprehensive care programmes, and therapeutic modalities such as home treatment and prophylaxis. There is clear evidence that life expectancy has increased for individuals with hemophilia. In the early part of the last century, the prevalence of hemophilia was estimated to be only 4 per 100 000 males, while the prevalence in the 1990s was 13-18 per 100 000 [3]. More recent studies estimating life expectancy for individuals with severe hemophilia not infected with HIV in the period 1977-2001 have ranged from 63 years for the U.K., to 70 years (Netherlands) and 73 years (Canada) [4-6]. However, since improvements in hemophilia care have been relatively recent and due to the high mortality rate from bleeding and transfusion-transmitted infection, particularly HIV in past decades, there is, at present in many countries, a relatively small population of severely affected individuals with hemophilia at advanced age and thus, relatively little experience in managing age-related medical problems in this group of individuals.

Age-related medical problems

As much as 88% of the general population over the age of 65 years have one or more chronic medical condition [7] and for the first time, many countries have seen the emergence of a significant middle-aged and elderly population of persons with hemophilia. There is considerable interest in the potentially complex interactions between a tendency to bleed in these individuals and age-related medical problems such as cardiovascular disease, neoplasia, renal, and musculoskeletal disorders. To date there are little evidence-based data to guide management of acute and chronic medical problems in older adults with hemophilia, but there are an increasing number of studies seeking to explore future health issues in this population.

Cardiovascular disease

In developed countries, cardiovascular disease (CVD) is the leading cause of death [2,8] with ischemic heart disease (IHD) and stroke being the main contributors. The risk is greater with advancing age [9] and the extent to which the ageing pwh shares this risk of CVD has attracted considerable interest. Perhaps because of the prominent position of CVD as a cause of mortality and the particular dilemma posed by using antithrombotic agents in individuals with bleeding disorders, there appears to be more literature on this subject than for other age-related medical disorders.

Ischemic heart disease

Epidemiological studies

Ischemic heart disease is the main contributor to overall cardiovascular mortality. Most epidemiological studies of populations of pwh have concluded that the risk of IHD appears to be lower than for the non-hemophilic population with a standardized mortality ratio (SMR) ranging from 0.2 to 0.62 compared with the general population [4,5,9-13]. However, not all studies have consistent findings. Kulkarni et al. [12], in their review of data from a U.S. cohort, found that the prevalence of IHD was 15.2% in older individuals and concluded that this was similar to an age-matched control population of non-hemophilic subjects. Moreover, a large study from the U.S.A. reported an SMR of 3.0 for myocardial infarction, indicating an increased risk for pwh. There appeared to be no clear explanation. [14] A significant problem with these data was that they were decades old, were mostly retrospective, and suffered from the recognized disadvantages of cohort studies (e.g. biased reporting, small number of reported events, and lack of detailed information such as the severity of hemophilia). Another aspect relevant to this discussion is that the cohorts included a relatively small number of patients of advanced age.

These studies yield interesting information but it is clearly important to generate accurate data on the true risk of IHD in the hemophilic population so that appropriate health measures may be planned. Large, prospective, and detailed studies, probably through international collaboration, are needed to address this issue.

Atherosclerosis and hemophilia

There have been direct and indirect attempts to assess the extent of the underlying pathological cause of ischemic heart disease, atherosclerosis, in individuals with hemophilia. Dalldorf et al. [15], prompted by clinical reports of ischemic heart disease in individuals with hemophilia, undertook a small post-mortem study of five individuals with classic hemophilia who had died of various causes. They found patterns of atherosclerosis similar to that in non-hemophilic individuals and one subject who had died of severe, multi-vessel coronary artery disease. A later postmortem study of 14 individuals with hemophilia confirmed that there appeared to be no significant difference in the degree of coronary vessel occlusion compared with age-matched controls [16]. There have also been systematic screening studies of living hemophilic subjects for markers of atherosclerosis using ultrasound techniques to detect intima media thickening (IMT) and arterial plaques. Bilora et al. [17] found less evidence of atherosclerosis in their study group compared with controls and concluded that hemophilia offered some protection against ischemic heart disease. However, a later study by the same group found no significant difference in IMT between hemophilic subjects and controls and in addition, they reported the presence of endothelial dysfunction, a potential early marker for atherosclerosis, in their study group. [18] Another group, Sramek et al. [19] also found no significant difference in intima media thickening in their cohort of subjects with congenital bleeding disorders compared with controls. Of note, these studies were relatively small, did not confine their studies to severe hemophilia, and the median age of subjects was relatively young. There have been no studies in a large population of older hemophiliacs, the group most likely to be at risk of symptomatic disease, probably because, to date, there are so few individuals in this age group available for study.

Perhaps the most direct evidence of cardiovascular disease in hemophilia is the reports of clinical cases. There have been regular, small numbers of such reports over time and it appears that the motivation for publication was the view that such cases were unexpected. Small et al. [20] reported two cases of extensive atherosclerosis in severe hemophilia. One individual had a myocardial infarction after intensive replacement therapy and the other showed severe atherosclerosis at postmortem after dying from unrelated causes. Girolami et al. [21] reviewed all 42 published cases up to 2006 and noted that most occurred in older individuals and after intensive replacement therapy.

Risk factors for IHD in hemophilia

There have been several reports on the prevalence of risk factors for IHD in pwh, often with conflicting data. The risk factors for IHD in pwh appear to be the same as for the general population [12,22,23]. Hypertension, a recognized risk factor for CVD, has been studied in several cohorts and most reported a higher prevalence in pwh [12,13,22-25]. Although it is postulated that this may be linked with renal disease in hemophilia, it is not clear whether hypertension caused or was a consequence of renal disease. Hypercholesterolemia has also been

reported to be linked with IHD in hemophiliacs but by contrast, other studies have found that compared with controls, cholesterol levels are lower in pwh. It has been suggested that this latter observation may be a consequence of hepatitis C liver disease, but there are insufficient data from which to draw firm conclusions [13,23]. Diabetes has been reported to be increased in pwh [22,24] but this is not a consistent finding as others have found no difference compared with controls [12]. In addition, those studies that report increased prevalence offer no clear explanation and there is no clear evidence of increased obesity in older individuals with hemophilia [23]. Ageing pwh who are HIV positive may also be at higher risk for IHD because of highly active retroviral therapy (HAART). While it is recognized that non-hemophilic individuals on HAART therapy are at increased risk for myocardial infarction, in the absence of specific data it is not clear whether this risk is shared by pwh [25].

These studies demonstrate that atherosclerosis and IHD can and do occur in hemophilia. It may be that the severe deficiency of factor VIII or IX may offer relative protection against the final thrombotic insult in the narrowed arterial lumen that often precipitates the more severe manifestations of IHD. If so, then it may be prudent to exercise caution during intensive replacement therapy such as with major surgical procedures, particularly in elderly subjects and it may be preferable to use measures such as carefully controlled continuous infusion to avoid peaks of coagulation factor activity in this setting. This may be particularly important during replacement therapy in the setting of acute coronary syndrome [26].

Clinical management of IHD

Symptomatic ischemic heart disease appears to be increasing in hemophilia [27] at least in part because of an ageing population. Acute coronary syndromes (ACS) pose a particular challenge because of the need to consider the risk of bleeding when using antithrombotic therapy. There is a paucity of data from which to create guidelines for management of this situation. Most reports are of single cases. In general, the principle of management of these clinical cases is to correct the clotting factor deficiency by using factor replacement and then treating the patient as closely as possible to standard protocols for ACS. Recently, consensus guidelines have been published for this situation and have made recommendations specific for hemophilia such as avoidance of thrombolytic therapy, the use of bare metal stents for percutaneous coronary intervention, and the use of prophylaxis during dual anti-platelet therapy [27]. While such guidelines are likely to be useful to guide treatment of individual patients, it must be recognized that such guidelines are largely based on opinion rather than evidence and it is important that they should be reviewed and updated when more robust evidence emerges.

Valvular heart disease is also more prevalent in older populations [28] and it is likely that more cardiac surgery will be performed in older persons with hemophilia. Cardiac bypass has been performed safely in hemophilia [29] but requires careful planning and management. Valve prostheses should be of a material that does not necessitate anticoagulation.

The prevalence of atrial fibrillation, a major cause of stroke, is strongly correlated with advancing age [30]. The use of anticoagulant therapy in individuals with atrial fibrillation is very effective at reducing the risk of stroke but risk stratification models have not been applied to or validated for hemophilia. It is not clear to what extent hemophilia may protect against stroke and there are major practical issues in considering anticoagulant therapy in these individuals. Reports of thrombotic stroke in hemophilia are rare but this may be in part because there are so few older patients in the highest risk stratum.

Cancer

Cancer is another major cause of morbidity and mortality in the general population. It is estimated that one in three individuals develop cancer during their lives and the risk for many cancers is age-related [31]. There are two key issues for pwh: is the risk of cancer increased in hemophilia, and is the management of cancer more problematic in individuals with bleeding disorders?

The two situations where mortality is clearly increased are in those infected with HIV or HCV. The incidence of non-Hodgkin's lymphoma, basal cell cancer, and Kaposi sarcoma has been shown to be increased in HIV-infected individuals with hemophilia compared with non-infected pwh [32]. Since the introduction of HAART, the incidence and mortality in this group of individuals has declined [33], but there are few recent data as to whether advancing age may yet change this pattern. The risk

of hepatocellular carcinoma (HCC) is increased in chronic HCV infection and this is reflected in the fact that HCC is now a leading cause of death in pwh [34]. Furthermore, the risk of HCC is increased in older age [35].

There are conflicting data on the incidence of cancer in hemophilia in pwh without HIV and HCV. Many of the studies reporting on this had several potential sources of error. Mortality rates in the study populations were high from viral infections and bleeding, so that these individuals may not have lived long enough to develop cancer. A Dutch study looking at mortality in pwh in the period 1973-1986 found an excess of deaths from cancer, particularly lung cancer [9], and a small, more recent German study [36] found an almost four-fold increase in extra hepatic malignancy in their study group. This contrasts with several other studies that found no significant increase in malignancy in non-HIV and non-HCV-infected individuals with hemophilia [4,6,11,37,38]. These conflicting data again highlight the need for larger, prospective studies.

By virtue of advancing age, it is likely that more individuals with cancer will be encountered in clinical practice. Factor replacement therapy will clearly be necessary to cover diagnostic procedures such as biopsy or surgical procedures and should be relatively straightforward. However, there are few data to guide replacement therapy to prevent bleeding from tumours that shrink with chemotherapy or radiotherapy. Furthermore, it is not clear how intensive factor replacement needs to be to cover complications of chemotherapy such as thrombocytopenia. By contrast, will the use of intensive factor replacement therapy or prolonged, high-dose prophylaxis increase the risk of venous thromboembolism in this situation? The development of cancer in an older person with hemophilia is likely to be a complex medical issue.

Renal disease

Chronic kidney disease (CKD) is another important age-related medical issue. In the U.S.A., the prevalence of stage 3 or 4 CKD increases to 37.8% after the age of 70 years [39]. It appears that this is mainly caused by loss of renal mass, decreased renal blood flow, and other age-related morbidity such as diabetes, hypertension and drug-related toxicity [40]. Individuals with hemophilia have been reported as having a high risk of acute and chronic disease with the risk of death from renal failure as high as 30 to 50 times higher than the general population [9,14]. In these studies, a high proportion of cases were linked with HIV disease.

An extension of one of these studies examined the case records of >3000 pwh who had been admitted to hospital during the period 1993-1998 [40]. In this study, acute renal failure was found in 3.4/1000 males as opposed to 1.9/1000 for the general population, and chronic kidney disease was found in 4.7/1000, compared to 2.9/1000 for the general population. HIV disease and hypertension were strongly correlated with acute and chronic kidney disease in this cohort. Other risk factors were increased age, non-white race, inhibitors and kidney bleeds. Moreover, there were some potential sources of error in this study and larger, prospective studies are needed to confirm these data.

If kidney disease is more common in pwh and, as is already happening, a population at advanced age emerges, it is likely that more cases of end-stage renal failure will be seen. The successful use of dialysis in hemophilia has been reported and there has been discussion on the relative merits of different approaches. It has been suggested that peritoneal dialysis may offer advantages for pwh, as factor replacement therapy is often only required for the insertion of the peritoneal catheter but not for subsequent dialysis procedures. However, this may not be suitable for those with chronic liver disease or HIV disease because of the risk of infection and the concern of peritoneal hemorrhage. Hemodialysis has also been used successfully but may require both the administration of factor concentrate and anti-coagulation with heparin during dialysis. There is, as yet, little consensus on the optimal regime [39].

Musculoskeletal disease

Prophylaxis with factor concentrates has been shown, if started early enough, to reduce the burden of hemophilic arthropathy [41]. Many adults with severe hemophilia advancing into older age were not treated with prophylaxis as children and therefore have established joint disease and the associated burden of joint deformity, muscle weakness, and impaired proprioception [42,43]. Such conditions may cause difficulty with mobility, pain, increased risk of falls, and social isolation [22,42,43,44]. In

this subgroup of patients, the effects of advancing age may be significant as proprioceptive loss may worsen and the risk of falls increases substantially [22,44]. Intervention by targeted physiotherapy and strength training may be effective at maintaining mobility and reducing the risk of falls [22,43,44]. This may require a radical review of the range of physiotherapy services required for future comprehensive care for this age group.

Another consideration for this older group of pwh is the possible presence of osteoporosis [45]. The risk of osteoporosis has been shown to be increased in some studies of individuals with hemophilia. This may be associated with the risk of skeletal problems such as bone fracture and may make the replacement of joints more problematic [45,46]. A number of measures may be effective in reducing the risk and consequences of osteoporosis including physical exercise. This raises the issue over whether screening for osteoporosis should be undertaken in older pwh and whether there should be re-evaluation of physiotherapy services for hemophilia [46].

Although prophylaxis may prevent hemophilic arthropathy, it is unlikely to have an impact on the most common type of arthropathy in older individuals, i.e. degenerative or osteoarthritis. It has been estimated that by 2030, in the general population, the number of first time total knee replacements will increase by 673%, the number of total hip replacements will increase by 174%, and the number of surgical revision procedures will increase substantially [47]. Thus, the number of orthopedic surgical procedures may actually increase in the ageing hemophilic population and may involve joints less commonly affected by hemophilic arthropathy such as hips, shoulders and the spine [47].

Conclusion

The life expectancy for individuals with hemophilia is increasing and may approach that of the general population. Up-to-date estimates of the future demographics of hemophilia are needed to help plan appropriate comprehensive care and to estimate the financial resources required to support the expanding and perhaps more demanding population of pwh. In many countries, an older population with hemophilia is emerging and the coexistence of age-related morbidity may become the norm rather than a relative rarity. At present there is little experience in managing these conditions and little evidence-based information to guide clinicians. Given that the population is ageing slowly, and age-related medical complications are still relatively uncommon, it may take some time to generate high quality data. It is essential that international collaborative exercises be set up to address the future challenges posed by the ageing hemophilic population.

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