Haemophilia is a serious medical condition, resulting in prolonged or intensive episodes of bleeding. Given the rich vasculature of the eye, ocular complications are likely in this condition. This CET article gives a summary of haemophilia, with an emphasis on the ocular presentations that may be seen in both diagnosed and undiagnosed sufferers.

**Course code C-33847 | Deadline: November 29, 2013**

**Learning objectives**
- To obtain relevant history and symptoms for patients presenting with haemophilia (Group 1.1.1)
- To recognise the manifestations of ocular disease in haemophilia (Group 6.1.13)

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Introduction

Haemophilia is a collection of coagulopathies where the affected individual is unable to produce the correct protein factors required for blood clot formation, resulting in prolonged or intensive episodes of bleeding. Although the condition ranges in severity, it means that the slightest trauma has the potential for serious repercussions. Most presentations have a genetic cause, however, acquired forms have also been reported. The defect is commonly found on the X chromosome, leading to a much higher prevalence in males. The World Health Organisation (WHO) estimates that there are around 6,000 haemophiliacs in the UK. Whilst haemophilia affects the whole body, ocular complications are likely given the rich vasculature and high sensitivity of the eye.

The haemophilias

When a blood vessel is damaged, a complex repair process is initiated to stem the flow of blood and allow vessel repair to take place (see Figures 1 and 2). Haemophilia affects the intricate cascade of blood protein factor production. The type of haemophilia is dependent upon which coagulation factor is affected. Historically, the haemophilias were all considered to be one entity until detailed blood separation techniques allowed more in-depth analyses and categorisation. The most common form, with 5,400 sufferers in the UK, affects patients lacking Factor VIII (FVIII) and is termed haemophilia A. Haemophilia B, or Christmas disease, affects Factor IX (FIX) and is much rarer, with only 1,100 sufferers in the UK. Recent DNA analysis has shown haemophilia B to be the type that affected descendents of Queen Victoria. The rarest form, haemophilia C, or Rosenthal syndrome, affects Factor XI (FXI). This form is not always considered to be a ‘true’ haemophilia since it is an autosomal condition, affecting males and females equally.

Ocular complications

Haemophilia is relatively rare; consequently there are few epidemiological studies that focus on the ocular manifestations of the disease. The majority of ocular complications are traumatic or surgical in origin. This means that most cases fall under the care of ophthalmologists, however, there is still the potential for them to present in optometric practice.

Spontaneous episodes

Haemorrhaging is a common occurrence in haemophilia, causing 25% of ocular complications. While relatively innocuous for routine patients, subconjunctival haemorrhage in haemophiliacs can be much more severe, with the potential to develop into total peri-orbital haemorrhage within 24 hours. This can result in compression of the optic nerve and a marked reduction in vision.

Spontaneous haemorrhages have also been reported at other locations within the eye and adnexa. Serious cases may present with a rapid drop in vision due to macular haemorrhage and choroidal detachment. Patients such as these may be undiagnosed with a blood disorder at presentation and are at risk of death from cerebral haemorrhage, highlighting the importance of early diagnosis with the potential lack of any predisposing signs.

Prompt treatment in the case of patients with known haemophilia can significantly improve clinical outcomes. For example, extensive spontaneous optic disc haemorrhage may be treated effectively with a standard programme of blood factor replacement therapy before any adverse effect on vision occurs.

Hyphaema is commonly associated with haemophilia, mostly in response to direct ocular trauma or following surgery (see Figure 3). However, spontaneous cases have been reported in young infants, initiating haematological investigation and resulting in diagnosis of haemophilia.

Trauma-related episodes

The majority of ocular traumas involve the anterior segment, often presenting with hyphaema. Perhaps unsurprisingly, most traumatic incidents arise in children, where the diagnosis of haemophilia may not
Trauma does not have to be direct to the eye to create potential ocular problems. An incident was reported where a child presented with severe proptosis and chemosis, resulting in a sharp decline in vision and a relative afferent pupillary defect.\textsuperscript{19} History revealed that the patient had suffered a mild head trauma several days previously, and there was a resultant haemorrhage into the subperiosteal region on the scalp. Due to the contained space, the blood had caused a constriction of the optic nerve, highlighting the risks to the entire visual pathway. Careful consideration of history and symptoms to elicit all potential clues is vital. In this case, an orbital decompression was performed to relieve the pressure on the optic nerve, and the child was subsequently diagnosed with mild haemophilia B. Such injuries have the potential to cause devastating effects, and correct management is paramount.

Responses to trauma in haemophilia are not always immediate in their presentation. One case reported an undiagnosed haemophilic patient presenting with a decrease in vision following a fall and blow to the head.\textsuperscript{17} Examination revealed a small hyphaema and dense vitreous haemorrhage. Having been treated and discharged, the patient returned a week later with increased pain in the eye and an ultrasound scan revealed choroidal detachment and suprachoroidal haemorrhage. Questioning revealed that while he had sustained a severe injury in the Vietnam War, there was no other history of intense bleeding, despite living an active lifestyle. Subsequent haematology tests showed a mild deficiency in Factor VIII. Pathological examination showed evidence of several previous suprachoroidal haemorrhagic detachments. It is, therefore, possible that patients may present in routine ophthalmic practice with asymptomatic bleeds.

In the most severe cases, effects on the eye from haemophilia can result in enucleation. This is a severe outcome for the patient and still performed on occasion, despite surgical and medical procedures having improved over time. Urgency in diagnosing the cause allows for the correct treatment regimen to be commenced earlier and hopefully prevent this outcome.

Cases have been reported of infants presenting with retinal and cerebral haemorrhaging, initially suspected of suffering from Shaken Baby Syndrome.\textsuperscript{29} Further investigation found instead that the clinical signs were a result of haemophilia, demonstrating the importance of blood tests in preventing a potentially serious legal outcome.

**Surgical considerations**

With haemophiliacs, all surgical procedures carry an increased risk and considering its extensive vasculature, extra care must be taken when operating on the eye (see Figure 4). Paradoxically, the surgical risks for patients with mild haemophilia are greatest; these patients are much more likely to have a negative history of bleeding episodes and may even have tested negative on previous tests.\textsuperscript{14} This means that the first signs of a coagulopathy may occur on the operating table, posing an unexpected and serious complication. Such a case was reported in 2001 with a 75-year-old patient being treated for a long-standing corneal opacity.\textsuperscript{3} A penetrating keratoplasty was planned, alongside a routine cataract extraction. However, when the fixation ring was placed on the eye prior to the graft surgery, a progressively enlarging subconjunctival haemorrhage appeared which would not abate. After aborting the surgery, investigation revealed haemophilia, thought to be a mild age-related, acquired form. Only with this information could the surgery be performed and the correct pre-operative precautions initiated, namely factor-replacement therapy in the weeks leading up to the surgery.

Accounts have proven that a negative history is not indicative of a coagulopathy-free patient, as bleeding episodes can vary in intensity, even in patients who have had previous surgical procedures. Mild forms of haemophilia can be missed and in the case of haemophilia A, FVIII levels are known to be naturally higher in children, but also to rise in times of stress (such as when a child is taken for a blood test).\textsuperscript{14} This rise could potentially mask a mild deficiency, which may only come to light later.
Advances in surgical procedures themselves and also the use of cryoprecipitates (frozen factor replacements) before treatment to raise the required factor levels, means that previously contraindicated surgery is now possible. Cataract extraction is the most widely undertaken surgical procedure, performed on patients with known and undiagnosed haemophilia. In the case of diagnosed patients, surgery is usually uneventful, although the risks are greater for patients in the developing world, with limited resources to manage potential complications.

Blood factor replacement has been the standard therapy for haemophilia since the 1960s, although an increasing number of patients are reported to be developing an autoimmunity to this treatment. This means that it is possible to develop clinically unresponsive bleeding episodes during surgery, with potentially disastrous consequences. In these cases, an alternative blood factor may be required prior to surgical intervention. In short, haemophilia has become a consideration for surgery rather than a barrier.

Comorbidity
Haemophiliacs with coexisting disease can present as complex cases for the clinician. For example, cases of aniridia with associated weakness in iris vessels may present with spontaneous hyphaema and markedly elevated IOP. Further, individuals with haemophilia are susceptible to complications in other disease with a neovascular element, such as wet AMD.

Historically, poor selection and treatment of blood samples, plus the heavy usage of transfusions by people with haemophilia meant that they were highly susceptible to blood-borne pathologies such as HIV and Hepatitis C. In the US, half of those with haemophilia contracted HIV between 1981 and 1985. Interestingly, a six-year study comparing those with HIV due to haemophilia treatment and other HIV patients revealed that no patients with haemophilia developed the typical cytomegalovirus (CMV) retinitis found in 42% of the other HIV patients. They also failed to develop cotton wool spots or retinal haemorrhages, compared to 35% of sexually-acquired HIV patients. Haemophilia, therefore, may provide a protective mechanism against CMV retinitis.

Relevance to the optometrist
Most reports concerning the ocular effects of haemophilia are isolated cases with few epidemiological studies, so true figures of incidence are difficult to determine. The wide range of locations and patient demographics add to the difficulty in determining rates of incidence. Generally it appears that people with known haemophilia have a much better prognosis, especially when treated promptly. Ocular complications from haemophilia are unlikely to present in routine optometric practice, but an awareness of the condition and its effects are still important for the practitioner to understand.

Figure 3: Traumatic hyphaema - blood in the anterior chamber is a common presentation in haemophiliacs following ocular trauma. Image courtesy of Elsevier

Figure 4: The uveal vascular tunic. Image courtesy of Elsevier

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