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Review

Haemophilia B: Where are we now and what does the future hold?

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ABSTRACT

Research has been lacking on the natural history, complications, and treatment of haemophilia B, which is less common than haemophilia A and was recognized as a distinct clinical entity in 1947. Although the two diseases share the same clinical manifestations, they differ in causative mutation, risk of inhibitor development, and patient quality of life. Frequently debated is whether haemophilia B is as clinically severe as haemophilia A, with much of the published data on overall and haemophilia-specific health outcomes suggesting that haemophilia B may have a less severe clinical phenotype. However, although fewer haemophilia B than haemophilia A patients appear to experience bleeding, bleeds are just as severe. We review distinguishing characteristics of haemophilia B and its treatment, including management strategies for neonates, therapeutic approaches for patients who develop inhibitors, pharmacokinetics of factor IX concentrates administered as replacement therapy, and potential future treatments.

1. Introduction

Haemophilia A and haemophilia B are recessive, X-linked bleeding disorders characterized by deficiency or absence of coagulation factor VIII (FVIII) or IX (FIX), respectively [1–3]. Haemophilia B is much less common than haemophilia A, accounting for just 15–20% of the total haemophilic population [3–6]; according to the latest global report from the World Federation of Hemophilia (WFH; compiled in 2014), there are 28,775 patients worldwide with haemophilia B and 143,523 patients who have haemophilia A [7]. The two forms of the disease were historically thought to represent the same bleeding disorder, and it was not until 1947 that haemophilia B was recognized as a separate entity [4,8,9]. For some time after this, the condition was often referred to as "Christmas disease," after the name of the first patient examined in detail [8].

The classic manifestation of the haemorrhagic tendency in haemophilic individuals is bleeding into the joints and muscles [6]. The bleeding phenotype is typically categorized according to residual factor levels and is defined as severe (< 1% residual FIX), moderate (1–5% FIX), or mild (> 5 to < 40% FIX) [1,2,4,6,10]. The mainstay of treatment for haemophilia B consists of replacement therapy with plasma-derived or recombinant FIX (rFIX) concentrates, administered either on demand when bleeds occur or prophylactically in scheduled infusions [2].

Historically, therapeutic advancements for haemophilia B tended to lag behind those for haemophilia A [5]. However, recent developments in potential new therapies for haemophilia B [5] have placed this disease firmly back in the spotlight. This review provides an update on key aspects of haemophilia B, and its main objective is to consider how haemophilia B differs from haemophilia A in terms of disease characteristics, severity, patient quality of life (QoL), and risk factors for inhibitor development. Management strategies for specific groups of haemophilia B patients, FIX pharmacokinetics (PK), and future therapeutic options will also be discussed.

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Table 1
Clinical and molecular characteristics of haemophilia A and B [6,12,13,16,29].

Characteristics	Haemophilia A	Haemophilia B
Gene location	Xq28	Xq27.1-q27.2
Number of exons	26	8
Common clinical symptoms	Haemarthroses, muscle haematoma	Haemarthroses, muscle haematoma
Bleeding frequency (episodes/year)	12–30, severe patients	12–30, severe patients
Age at first joint bleed (years)	1.18 in severe patients	1.20 in severe patients
Most frequent FVIII/FIX gene defects	Intron 22 inversions	Missense mutations
FVIII/FIX in vivo recovery (U/dL)/(U/kg)	1.5–2.0	0.8–1.0
FVIII/FIX half-life (hours)	8–12	18–24
Inhibitor incidence	~30–50%	< 5%
Anaphylaxis	Rare, not associated with inhibitor development	Often associated with inhibitor development
ITI success	60–80% of cases	< 50% of cases
Nephrotic syndrome	Not reported	May complicate ITI course

FVIII, factor VIII; FIX, factor IX; ITI, immune tolerance induction.

2. How does haemophilia B differ from haemophilia A?

2.1. Disease characteristics

Clinically, haemophilia A and haemophilia B are often considered indistinguishable and have often been thought of as a single disorder [11,12]. Both are caused by deficiencies in an endogenous coagulation factor critical for the intrinsic coagulation pathway, and both show X-linked inheritance [3,4,6,13,14] (Table 1). Each is characterized by a prolonged activated partial thromboplastin time and recurrent musculoskeletal bleeds [3,4,6,13,14], and treatment in both cases involves replacing the missing coagulation factor [6,13].

The pattern of underlying genetic mutations is often less severe in haemophilia B than in haemophilia A, with missense mutations occurring more frequently than null mutations [4,13]. As a result, severe disease is less common in haemophilia B (35% of patients versus 45% in haemophilia A) [4]. Coagulation factor PK also differs between the two subtypes of haemophilia: the half-life of FIX is longer (approximately 18–24 h) than that of FVIII (approximately 8–12 h), while recovery is lower [15,16] (Table 1). Furthermore, fewer than 5% of patients with haemophilia B develop neutralizing antibodies (inhibitors) against infused coagulation factor, compared with approximately 30–50% of patients with haemophilia A [6,13,17] (Table 1).

Inhibitor development in haemophilia B may be complicated further by the development of severe allergies (particularly anaphylactic reactions) against FIX concentrates, a phenomenon that is rarely seen in haemophilia A [13,18–20] (Table 1). The occurrence of allergic reactions further hinders attempts to eradicate the inhibitor through immune tolerance induction (ITI) and also complicates treatment with plasma-based bypassing therapy. Another serious and unique complication that may arise from treating haemophilia B patients who have anti-FIX inhibitors (Table 1) is the development of nephrotic syndrome, which may occur during ITI in association with an allergic phenotype [18,20].

2.2. Is haemophilia B less severe than haemophilia A?

It is often suggested that haemophilia B is less severe than haemophilia A and is associated with better long-term outcomes [11,12,21,22]. The current literature on overall health, bleeding frequency/severity, joint disease, and prophylaxis and factor consumption is briefly reviewed in Sections 2.2.1–2.2.4 in an effort to shed some light on this debate.

2.2.1. Overall health

Three key studies have assessed various measures of overall health in patients with haemophilia A or B. Darby et al. reported mortality data from 6018 patients with haemophilia A (n = 4874) or B (n = 1144) registered with the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) database; when accounting for inhibitor status, all-cause mortality for all disease severities did not differ significantly between haemophilia A and haemophilia B [23].

Across 178 hospitalizations in 58 patients from haemophilia treatment centres (HTCs) in the United States, Wong et al. found that there was no significant difference in mean length of hospital stay between patients with haemophilia A (5.6 days) and haemophilia B (5.3 days; p = 0.96) [24].

Finally, Chambost et al. studied the circumstances of diagnosis in a French cohort of 599 haemophilia patients (haemophilia A, n = 512; haemophilia B, n = 87) [25]. Haemophilia A was diagnosed earlier than haemophilia B (7.6 versus 8.7 months), but the difference was significant only for moderate disease. In addition, there was no significant difference in the proportion of haemophilia A and B patients diagnosed as a result of bleeding (60.7% and 55.6%, respectively; p = 0.20).

Together, these data suggest that the severity of haemophilia A and B cannot be reliably distinguished based on overall health outcomes.

2.2.2. Bleeding frequency/severity

Although recurrent bleeding is the hallmark of both haemophilia A and B, bleeding frequency may differ between the two forms of the disease [26–28]. In a single-centre, retrospective chart review by Nagel et al., bleeds occurred more frequently in patients with moderate-to-severe haemophilia A (n = 68; 14.4 bleeds/patient/year) than in those with moderate-to-severe haemophilia B (n = 20; 8.63 bleeds/patient/year) [27]. Similarly, when evaluated by the Hemophilia Severity Score (HSS), patients with severe haemophilia A were found to have a higher annual incidence of joint bleeds than patients with severe haemophilia B, although this did not reach statistical significance [28].

Recent data from the European Paediatric Network for Haemophilia Management (PedNet) Registry showed that children with severe haemophilia A (n = 582) and B (n = 76) did not differ significantly in age at first exposure to clotting factor (0.81 versus 0.88 years; p = 0.20), age at first bleed (0.82 versus 0.88 years; p = 0.36), or age at first joint bleed (1.18 versus 1.20 years; p = 0.59) [29]. However, this study excluded non-bleeding patients, which may explain why it did not find any differences between haemophilia A and B. Furthermore, because many children with haemophilia start prophylaxis before the first bleed, age to first joint bleed may not be a reliable indicator of disease severity.

2.2.3. Joint disease

Existing evidence regarding the relative frequency of arthropathy in haemophilia A and B is inconclusive. Soucie et al. examined the range-of-motion (ROM) of 10 joints (hips, knees, shoulders, elbows, ankles) in 4343 young men with haemophilia A (n = 3502) or haemophilia B (n = 841) registered in the Universal Data Collection (UDC) project [30]. Haemophilia A and B patients with severe or mild disease had