Neonatal haemophilia – a guide to recognition and management

Although haemophilia is the most common type of inherited bleeding disorder to present in the neonatal period, making a diagnosis can be difficult. This article will explore the clinical presentation, diagnosis and treatment of neonatal haemophilia.

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Key points

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1. Haemophilia is an important cause of bleeding in the well neonate.
2. In carrier mothers the aim should be for a normal delivery in a haemophilia centre.
3. Significant bleeds need urgent treatment with recombinant factor VIII.
4. Delay in diagnosis is common but can be avoided by prompt recognition and investigation of abnormal bleeding.

Although haemophilia might not be considered a common condition in neonates, it is the most common inherited bleeding disorder to present in the newborn period[1]. The significant proportion of sporadic cases, the variety of possible bleeding patterns and the difficulty in recognising and investigating neonatal bleeding problems can lead to a delay in diagnosis. Early diagnosis allows for parent education, appropriate treatment and prophylaxis and may also minimise disability caused by later joint and muscle bleeds[2]. This article will explore the clinical presentation, diagnosis and treatment of haemophilia in the newborn.

What is haemophilia?

Haemophilia is an X-linked recessive bleeding disorder that occurs in 1 in 5,000 males, has a worldwide distribution and affects all racial groups[3]. The condition is caused by defects in the genes responsible for the production of proteins important in the blood clotting cascade. In haemophilia A, which represents 80-85% of cases[3], defects occur in the gene responsible for the production of a protein called factor VIII (FVIII), whereas the defect in haemophilia B affects factor IX (FIX) production, though the two conditions are clinically indistinguishable[4].

If a female (karyotype XX) inherits an abnormal copy of the haemophilia gene from one parent, she becomes a carrier but is not clinically affected because she has a second normal copy of the gene on her other X chromosome. However, a male (karyotype XY) inheriting an abnormal copy will always be affected as he only has one X chromosome. Although haemophilia can be inherited, it is important to remember that around a third of cases occur due to a sporadic mutation of the gene, meaning there will be no family history of the condition[1].

So how does a deficiency of FVIII or FIX lead to a bleeding problem? Haemostasis (blood clotting) is a complex process during which blood vessels, platelets and clotting factors interact to minimise bleeding following tissue injury. Primary haemostasis involves platelets interacting with the injured vessel wall to form a primary haemostatic plug. Secondary haemostasis occurs when clotting factors are sequentially activated and results in the production of thrombin, needed for clot formation[5]. In haemophilia, primary platelet plug formation is normal but the deficiency of FVIII or FIX causes impaired secondary haemostasis resulting in delayed clot formation and susceptibility to continued bleeding as a result of clots being abnormally friable. The severity of the condition is primarily determined by plasma levels of the deficient factor, which are expressed as percentage activity, with 100% activity being equivalent to 1 unit/mL of factor and normal values ranging from 50-150%[6]. Severe haemophilia (<1% activity) almost always presents in early life[2] with frequent spontaneous bleeding. Moderate haemophilia (1-5% activity) can present with severe bleeding following injury and occasional spontaneous bleeds whereas mild haemophilia (>5% activity) may remain undiagnosed or only present with bleeding after injury or surgery, though bleeding can still be severe[7].

Presentation of haemophilia in the neonate

Bleeding in neonates is not an uncommon problem. Pulmonary haemorrhage, gastrointestinal bleeding, bleeding from venepuncture and intraventricular haemorrhage occur relatively frequently in preterm infants or term infants with infection or hypoxic-ischaemic injury. In these circumstances, bleeding usually

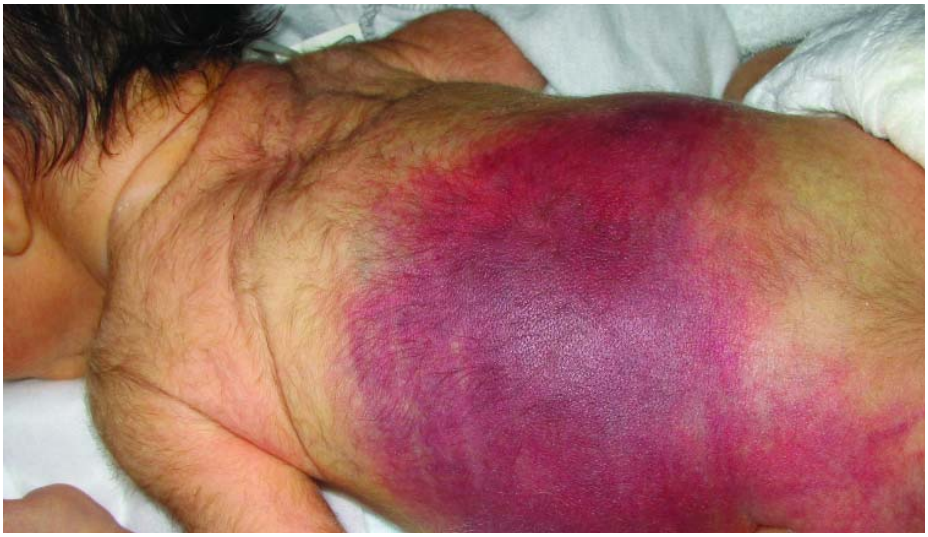

FIGURE 1 Spontaneous haematoma.

occurs as a result of acquired conditions such as thrombocytopaenia or disseminated intravascular coagulation (DIC), and infants are often unwell. In contrast, haemophilia often presents as unexplained bleeding in an otherwise well infant[8].

So how can an infant with haemophilia be identified? In some infants, there will be a family history of haemophilia in which case the mother ought to have had her carrier status tested and the infant will be tested routinely after birth. However, in cases where there is no family history, diagnosis will be made after an iatrogenic or spontaneous bleed, with 30-60% of individuals being diagnosed within the neonatal period[2,3,9]. Since identification of cases after a bleed still represents a large proportion of diagnoses and bleeding patterns are different from those in older children (who present with joint and muscle bleeds), identification of bleeding patterns in neonatal haemophilia remains important[9].

A variety of presentations have been described in the literature but as much of the data is from case reports, it can be difficult to identify the true incidence of each presentation. However, the reported presentations can be divided into spontaneous or iatrogenic bleeds, with some reporting iatrogenic bleeds as being more common as a presenting bleed in infants under one month of age and spontaneous bleeds being more common later in infancy[9].

Spontaneous bleeds

Intracranial haemorrhage

Although the true incidence of intracranial haemorrhage (ICH) is probably unknown due to under-reporting and misdiagnosis, it is estimated to occur in 1 to 4% of neonates with haemophilia[3]. ICH in the neonatal period is thought to be related to birth trauma, so usually presents within the first week of life with signs of acute hypovolaemia, non-specific symptoms such as lethargy and vomiting or more specific neurological signs such as hypertonia or seizures[4]. Although cranial ultrasound detects some cases, CT may be required to identify subdural or posterior fossa bleeds. The diagnosis is important because 40-60% of infants with haemophilia and an ICH go on to have neurological sequelae including seizures, learning difficulty or persisting neurological signs[10,11]. While some recommend that FVIII levels be checked in all term male infants presenting with an ICH[12], even when this is done, an alternative initial diagnosis (such as sepsis or meningitis) may be made, despite clotting screen results being consistent with a diagnosis of haemophilia[11].

Extracranial bleeds

Bleeding outside the cranial cavity can occur below the periosteum lining the outside of the skull bones (cephalohaematoma) or below the galea aponeurotica (subgaleal), a thin tendonous sheath in the scalp. Although neurological sequelae are unusual in extracranial haemorrhage (ECH), large amounts of blood can be lost, leading to a mortality rate of up to 22% in subgaleal bleeds[13], so prompt recognition and resuscitation are required. ECH can occur concurrently with an ICH, the cumulative incidence of ICH and ECH being reported as 3.58% in the neonatal period[10].

Other sites of spontaneous bleeding

It is less common for newborns with haemophilia to present with spontaneous bleeding elsewhere but a variety of other sites of bleeding have been reported. Umbilical bleeding can be seen in haemophilia but is more common in vitamin K deficiency, factor XIII deficiency or low fibrinogen[14]. Rarer presentations include spontaneous gastrointestinal bleeding[15], intrahepatic bleeding[16], splenic haematoma and rupture[17,18], adrenal bleeding[19] and spontaneous superficial haematoma (**FIGURE 1**).

Iatrogenic bleeds

Puncture bleeds

As haemophilia causes a delay in clot formation, routine procedures may result in excessive bruising or haematoma formation. Problems can occur after venepuncture, intramuscular injection (vitamin K administration or immunisation), arterial puncture or heel prick blood sampling. Excessive bleeding after any of these procedures should warrant consideration of haemophilia or another clotting disorder as a diagnosis.

Circumcision

In some reviews, post-circumcision bleeding is cited as a common presentation of haemophilia, accounting for up to 30% of cases[3], though it is important to remember that circumcision is performed more commonly in the US than in Europe[2]. Nevertheless, post-circumcision bleeding ought to be investigated if it is deemed excessive.

Management of pregnancy in carrier mothers

If a mother is known to be a carrier of haemophilia, pregnancy and labour can be managed in a way which reduces the risk of adverse events for the mother and baby. Issues to consider include place of delivery, antenatal counselling and diagnosis, management of delivery and care of the infant after birth.

Place of delivery

Mothers who are known carriers of haemophilia should be booked to deliver in an obstetric unit at a haemophilia centre for both their own and their child's benefit. Carrier mothers, although not normally clinically affected, may have relatively low FVIII or FIX levels,

Condition	PT	APTT	Fibrinogen	Platelets
Vitamin K deficiency	↑	normal	normal	normal
Haemophilia	normal	↑	normal	normal
Disseminated intravascular coagulation	↑	↑	↓	↓
Liver disease	↑	↑	normal / ↓	normal / ↓

TABLE 1 FBC and coagulation screen results for commoner causes of neonatal bleeding.

predisposing them to haemorrhage which may warrant treatment with recombinant FVIII[20]. Male offspring will need factor levels checking after birth and affected infants could need urgent treatment with recombinant FVIII, which is only available at haemophilia centres.

Antenatal counselling and diagnosis

All known carrier mothers should be counselled antenatally, or even preconceptually regarding the risk of haemophilia in the newborn and can be offered prenatal diagnosis. In the first trimester, fetal tissue can be obtained by chorionic villus sampling and tested for the common genetic mutations. Similarly, fetal cells obtained by amniocentesis can be tested in the second trimester. At this stage it is also possible to sample blood from the umbilical vein – this has the advantage of providing both a diagnosis and an indication of the likely severity of disease, as fetal plasma FVIII levels can be measured.

Delivery

Management of labour and delivery of carrier mothers should be aimed at reducing the risk of haemorrhage in the mother and baby by avoiding perineal trauma and invasive procedures, such as fetal scalp blood sampling. A retrospective review of mode of delivery and neonatal bleeding reported that the risk of ICH following normal delivery is small, that vacuum extraction is a risk factor for bleeding and should be avoided, but that elective caesarean section cannot eliminate ICH or other serious bleeding[21]. Consequently, many centres aim for a normal vaginal delivery, with early recourse to caesarean section should labour become prolonged or complicated[20]. However, even when carrier status is known and delivery guidelines followed, severe haemorrhage can still occur[22].

Management of infants after birth

After birth, male infants should be tested for haemophilia, preferably by factor assays carried out on cord blood, thus avoiding the risk of iatrogenic bleeding following venepuncture. Venepuncture and heel prick blood sampling should be avoided if at all possible with some centres recommending the use of oral rather than intramuscular vitamin K. Female infants have a 50% chance of being a carrier, but testing would normally be deferred until the child is competent to consent themselves.

Management of suspected cases of neonatal haemophilia

When haemophilia is suspected because of a previously unidentified family history or a spontaneous or iatrogenic bleeding episode, it is important that the infant is investigated, that bleeding episodes are treated and that appropriate follow-up is arranged.

Diagnosis

Although the haemostatic system in neonates is relatively immature, nearly all bleeding disorders can be diagnosed using simple screening tests, provided results are interpreted using gestation and age-specific values[1,4]. All neonates with a suspected bleeding problem should have bloods sent for a full blood count (FBC), prothrombin time (PT) and activated partial thromboplastin time (APPT), with a fibrinogen test being requested if results are abnormal[5]. FBC will identify infants with a low platelet count, though bleeding problems secondary to a low platelet count are rare in the neonate[4]. PT measures factors II, V, VII and X and APTT measures a large range of factors (II, V, VIII, IX – XII) but is particularly sensitive in identifying FVIII deficiency[5].

In haemophilia, the APTT is prolonged but PT, fibrinogen and platelets are normal (**TABLE 1**). Similar results can be obtained if blood is sampled from heparinised lines, though a normal reptilase time confirms heparin contamination[4]. Diagnosis is confirmed by FVIII and FIX assays. In haemophilia A, the diagnosis can be made at birth because factor VIII levels are within the adult range in both term and preterm babies[14]. In the case of haemophilia B, diagnosis of severe cases is possible, but factor IX levels in mild cases overlap with the normal newborn range, so definitive diagnosis may not be possible until around six months of age[14]. Inherited disorders affecting other factors are extremely rare and need only be considered if FBC, PT, APTT and fibrinogen results have not elicited a diagnosis.

Treatment of bleeding episodes

If the diagnosis of haemophilia is suspected it is important to liaise as soon as possible with a haematologist and send bloods urgently for a clotting screen (APTT, PT and fibrinogen) and factor assays. However, whilst awaiting results, the primary aim must be to treat the consequences of any bleed and attempt to prevent further bleeding. Significant haemorrhage may warrant transfusion of blood and fresh frozen plasma (FFP), or cryoprecipitate can be given in an attempt to minimise bleeding[4], though there are only small amounts of clotting factors in FFP. Some authors advocate the administration of a prophylactic dose of recombinant FVIII prior to diagnosis where factors such as a family history of haemophilia make the diagnosis likely[22].

For significant bleeds, such as ICH or ECH, up to two weeks of treatment with replacement FVIII will be needed[4], with the aim to raise plasma levels to at least 50% of normal. A number of replacement factors are available but recombinant FVIII is recommended as it poses the lowest risk of viral transmission, though the paucity of evidence regarding pharmacokintics in infants and children means treatment regimes are largely adapted from those for adults[1].

Discharge planning and follow-up

Once a diagnosis of haemophilia has been made in a newborn infant, it is essential that the family have early contact with the local haemophilia team. They will need written information about the diagnosis and need to know the signs and symptoms of intracerebral bleeding so they are able to seek advice early. Liaison with the GP and health visitor is important and the family need to have details of how to contact the haemophilia centre should they need any advice. Hepatitis B vaccination is recommended[14] and parents need to know

to avoid giving their child non-steroidal anti-inflammatory medication as it can affect platelet function and exacerbate bleeding tendency. If this is the first case in the family, parents may also need referral for genetic counselling, usually undertaken at a later date.

Current controversies in management

The fact that intracerebral haemorrhage has sequelae including severe brain injury raises the question of whether such bleeding could be prevented or detected at an earlier stage, allowing for the possibility of more prompt and effective treatment[23].

Routine cranial ultrasound scanning

Although intracerebral bleeding probably has a low incidence in newborn infants with haemophilia, the high risk of long term neurological sequelae has led some authors to advocate a routine cranial ultrasound scan in any neonate diagnosed with haemophilia[22]. Presumably, if intracranial bleeds were detected early, treatment with recombinant factor VIII could be commenced with the hope that bleeding would be limited and outcome would improve. However, there are difficulties with performing scans on all babies diagnosed with haemophilia in the newborn period.

Cranial ultrasound scanning is non-invasive and relatively easy to perform, but is poor at detecting subdural haemorrhage, a common type of bleed in babies who have an intracerebral bleed in the first month of life. Also, it might be difficult to decide on the timing of scans. Although early intracerebral bleeds are presumed to be related to the process of delivery, the mean age at diagnosis of neonatal ICH and ECH has been quoted as 4.5 days[10] and it is unclear whether all would have been detected if scanned on day one[23]. Some authors recommend cranial ultrasound scanning in the first hours after birth if delivery has been traumatic[14] and a recent survey of UK practice confirms that the issue is unresolved, as 40% of centres scan all babies, 40% scan those when delivery was prolonged or instruments were used and the remaining 20% scan only those babies who show clinical signs of ICH[23].

Prophylactic factor VIII post-delivery

A single dose of recombinant FVIII is thought to provide normal haemostasis for 24 hours and some haemostatic efficacy for up to 72 hours. Some authors recommend it is given after birth in an attempt to prevent or decrease brain injury caused by ICH[22]. Although this idea seems attractive, there are concerns that this strategy may have adverse affects. Around 25-30% of haemophilia A patients develop FVIII inhibitors after exposure to FVIII concentrate (meaning alternative treatment is required for prophylaxis and treatment of bleeding episodes)[6,24]. There is some evidence that starting replacement therapy very early in life might increase the risk of inhibitor formation[24], though the role of confounding factors such as type of genetic mutation needs further evaluation[25]. In the UK, there is considerable variation in practice with 20% of centres considering giving short term prophylactic FVIII to all infants with haemophilia and 50% considering its use where delivery was traumatic or prolonged[23].

Summary

Haemophilia is the most common inherited bleeding disorder to present in the neonatal period but diagnosis is often delayed. A family history of the condition, present in two thirds of cases, should prompt testing of newborn males. In the absence of family history, cases will be identified after a spontaneous or iatrogenic bleeding episode, the patterns of which are different in the neonatal period as compared with patterns of bleeding in children and adults. Although the haemostatic system is immature in the neonate, a diagnosis of haemophilia A or moderate to severe haemophilia B can still be made, allowing for prompt treatment of significant bleeds and early contact between the family and the local haemophilia team. The current focus in neonatal haemophilia management is on whether the adverse neurological consequences of intracranial haemorrhage can be lessened by routine cranial ultrasound or prophylactic FVIII.

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