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# Retinal hemorrhage and bleeding disorders in children: A review

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ABSTRACT

*Background:* Retinal hemorrhages (RH) are a common manifestation of abusive head trauma (AHT) resulting from acceleration-deceleration injury with or without blunt impact. Evaluation of a child with RH requires careful consideration of these differential diagnoses. The extent to which coagulopathy alone can cause RH would be useful to understand as coagulopathy may accompany AHT.

*Objective:* In this systematic review, we sought to identify whether coagulopathies have been reported with RH similar to those of AHT.

*Methods:* We performed a literature search for ocular manifestations of bleeding disorders in children less than 18 years old. We included clotting factor deficiencies, vitamin K deficiency, platelet function abnormalities, thrombocytopenia, disseminated intravascular coagulation (DIC), and trauma induced coagulopathy (TIC). We included only pediatric reports of intraocular bleeding or documented eye examinations that indicated no hemorrhages. We then re-examined cases for ocular and systemic findings that could potentially mimic abuse.

*Results:* Our initial search yielded 816 results. Sixty-one articles met our inclusion criteria. Of these, there were 32 children within the AHT age range (less than 5 years old) who had RH and concomitant coagulopathy. Only 5 cases might potentially be confused for abuse. Of these, no classic characteristics of RH from abuse such as retinoschisis or retinal folds were found. Systemic features were inconsistent with AHT.

*Conclusions:* The presence of coagulopathy alone does not rule out the possibility that the child has been abused. Coagulopathy alone has not been reported as an etiology of RH that are consistent with AHT, especially when other findings are present.

## 1. Introduction

Abusive head trauma (AHT) refers to any form of head trauma that is a result of child abuse (Christian, Block, Committee on Child, A., Neglect, & American Academy of, & P., 2009). Retinal hemorrhages (RH) are particularly characteristic of AHT caused by repetitive

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acceleration-deceleration injury with or without blunt head impact (Christian et al., 2009). The incidence of AHT ranges from 16.1 to 33.8 reported cases per 100,000 infants per year (Barlow & Minns, 2000; Ellingson, Leventhal, & Weiss, 2008; Keenan et al., 2003; Minns, Jones, & Mok, 2008; Sills, Libby, & Orton, 2005). AHT is most common among in children in the first year of life, with the overwhelming majority of cases occurring before 3 years of age (Barlow & Minns, 2000; Feldman et al., 2001; Jayawant et al., 1998; Keenan et al., 2003). Visual outcomes of AHT may be devastating (Levin, 2010).

Evaluation of a child with RH requires careful consideration of all differential diagnoses before a determination of etiology is made. Several reports describe cases in which a child with a bleeding disorder was initially diagnosed as AHT (Brousseau, Kissoon, & McIntosh, 2005; Fenton, Sirotnak, & Handler, 2000; Gordon, Prakash, & Padmakumar, 2008; Harley, 1997; Newman, Jalili, Kolls, & Dietrich, 2002; O'Hare & Eden, 1984; Taylor, 1982; Wetzel, Slater, & Dover, 1995; Wheeler & Hobbs, 1988). Victims of AHT may have coagulopathy due to brain injury or other terminal events as well as anemia. Other hematologic abnormalities, such as von Willebrand disease (VWD), may be present by coincidence. Children with underlying pre-existing coagulopathy may also be abused. Careful consideration of the possible attribution of RH to these etiologies is essential to avoid either false negative or false positive determinations of diagnosis with regards to AHT.

The appropriate diagnosis for the cause of RH in childhood is of critical importance. The literature provides an extensive evidence base that can assist in the establishment of an accurate etiology. This review addresses the evaluation of the etiology of RH in the context of bleeding disorders.

## 2. Methods

A literature search was conducted using Pubmed using the search terms for coagulopathy disorders ("fibrinogen deficiency", "factor I" through "factor XIII deficiency", "prothrombin deficiency", "Owren disease", "hypoprothrombinemia", "parahemophilia", "proconvertin deficiency", "hemophilia A" through "hemophilia C", "antihemophilic factor a deficiency", "Christmas disease", "Stuart-Prower factor deficiency" "Hageman factor deficiency", "fibrin stabilizing factor deficiency", "von Willebrand disease", "VWD", "angiohemophilia", "vitamin K deficiency", "hemorrhagic disease of the newborn", "platelet function defect", "Hermansky-Pudlak", "Glanzmann thrombasthenia", "Wiscott-Aldrich", "Bernard Soulier", "Chediak-Higashi", "thrombocytopenia", "ITP", "idiopathic thrombocytopenic purpura", "hemolytic uremic syndrome", "neonatal alloimmune thrombocytopenia", "disseminated intravascular coagulation", and "DIC") in combination with terms related to pediatric ophthalmology ("children", "child", "infant", "neonate", "pediatric", "eye", "ophthalmic", "ophthalmology", "ocular", "retinal", "retina", "retinal hemorrhage", "intraocular", "orbit", "orbital", "retinoschisis"). No exclusions were placed on date of publication or study design. Preference was given to articles in English and French, though translation was obtained wherever possible when articles covered relevant topics. The initial search yielded 816 results. Titles and abstracts were screened based on relevance. Reports on coagulopathy were included based on presence of intraocular bleeding (RH, vitreous hemorrhage, hyphema) or documentation of an eye examination that indicated no hemorrhages. Titles were excluded if they only reported adult cases. We also pursued secondary citations from relevant papers. Fifty-four articles met our criteria. In addition, we screened articles from the senior author's (AVL) personal database of 3,208 citations largely related to retinal hemorrhage. From this library, and additional 7 articles met our criteria, yielding a total of 61 articles. We report all ocular examination findings from eligible studies or if full examination was not completed, this was noted. We also included articles outside of our inclusion criteria if they were relevant to our discussion, including coagulopathy cases with non-ocular findings that may mimic abuse and children older than 5 years who showed intraocular hemorrhage. Cases of patients in the common AHT age range (under the age of

**Table 1**
Abuse eliminated outright*.

| Report | Age | Diagnosis | Eye Findings |
|---|---|---|---|
| *Geraissate 2014* | 23 months | Hemolytic uremic syndrome | RH (bilateral)<br>Cotton-wool spots<br>Macular edema |
| *Hendrickson 2010* | 8 months | Malabsorption | Scattered RH (Bilateral)<br>Scattered preretinal RH (Bilateral)<br>Exudative retinal detachment (unilateral) |
| *Moussa 2017* | 3 years | Dyskeratosis congenita | Single unilateral subretinal hemorrhage<br>Cotton wool spots<br>Retinal vessel sclerosis |
| *Rusell-Eggit 2000* | 7 weeks | Hermansky-Pudlak syndrome | RH restricted to the posterior pole<br>Left = single RH<br>Right = dozen subhyaloid, intraretinal, and subretinal hemorrhages |
| *Sturm 2010* | 1–3 years | Hemolytic uremic syndrome | Dot and flame-shaped RH (bilateral and unilateral)<br>Cotton-wool spots |
| *Tarau 2019* | 2 months | Vitamin K deficiency | Intraretinal and preretinal hemorrhages confined to posterior pole (unilateral)<br>White centered hemorrhages (unilateral)<br>Peripapillary hemorrhage |
| *Viola 2013* | 5 years | Disseminated intravascular coagulation | Superficial RH over fovea (unilateral)<br>Macular and peripapillary areas of ischemic retinal whitening (bilateral) |

* Reasons abuse eliminated outright: Cotton wool spots, exudative retinal detachment and/or obvious systemic findings suggesting another diagnosis (although abuse cannot be ruled out in Rusell-Eggit).

5) with coagulopathy and RH were further reviewed, in particular to investigate whether these children were evaluated for possible child abuse. We also sought to identify and adjudicate whether there were other ocular or systemic features that would allow ready dismissal of a concern about abuse.

## 3. Results

All eligible articles were reviewed, and specific case presentations for each coagulopathy are summarized. A summary of cases within the usual AHT age range (<5 years old) is provided in Tables 1–4. Table 1 lists cases in which abuse could be eliminated outright. Table 2 lists instances where RH was non specific to etiology or could not be distinguished from birth RH. Cases listed in Table 3 do not provide enough information to rule in or rule out abuse. Finally, Table 4 lists all cases found in our literature review which could be potentially confused for abuse.

### 3.1. Clotting factor deficiencies

The interaction of circulating clotting factors form a cascade, which may be divided into intrinsic and extrinsic pathways (Fig. 1). Activation of either the intrinsic or extrinsic pathways leads to the activation of the common pathway.

a) **Fibrinogen (Factor I).** Action of thrombin on fibrinogen results in the formation of a fibrin clot, which is further stabilized by the cross-linking of activated Factor XIII (XIIIa). Fibrinogen defects will impede the final step of the common pathway. Diagnosis of a fibrinogen disorder is made by an elevated thrombin time and decreased fibrinogen level and/or activity. Decreased levels of fibrinogen secondary to congenital fibrinogen abnormalities, such as afibrinogenemia, hypofibrinogenemia or dysfibrinogenemia, are relatively rare and account for only 7% of rare bleeding disorders (disorders other than hemophilia or VWD) (*World Federation of Hemophilia Report on the Annual Global survey 2009, 2011*World Federation of Hemophilia Report on the Annual Global survey, 2011*World Federation of Hemophilia Report on the Annual Global survey 2009, 2011*). The estimated prevalence of each congenital fibrinogen disorder is approximately 1 per 1,000,000 individuals (Acharya & Dimichele, 2008).

Children with afibrinogenemia have a severe bleeding diathesis, with 85 % experiencing umbilical cord bleeding and 10 % experiencing bleeding within the central nervous system (CNS) (Peyvandi, 2012). Afibrinogenemia may also manifest with muscle hematomas (72 %) and hemarthrosis (54 %) as well as epistaxis and oral cavity bleeding (>70 %) (Peyvandi, 2012). Hypofibrinogenemia in children usually only causes bleeding in response to trauma (Acharya & Dimichele, 2008; Peyvandi, 2012). Clinical presentation of dysfibrinogenemia, is highly variable. Bleeding occurs in only approximately 25 %. Thrombosis, primarily deep vein thrombosis, thrombophlebitis, and pulmonary embolism, has been reported in approximately 20 % (Peyvandi, 2012).

Few cases describe RH in children in the context of low fibrinogen levels. Marshman et al. (Marshman, Adams, & Ohri, 1999) report the case of a 36 day old male infant born at 27 weeks gestation. Bilateral intraretinal hemorrhages with unilateral subretinal hemorrhages was observed on routine assessment for retinopathy of prematurity (ROP). The infant was examined the following day at which time bilateral vitreous hemorrhages were also observed. No comment was provided on RH severity or location. The neonate had remained resident in a special care nursery from the time of birth and there was no evidence to suggest non-accidental injury. Although the child did have clinically prolonged bleeding, decreased plasma fibrinogen (0.7 g/L) and thrombocytopenia (20 $\times 10^9$/L), given the baby's age (a time at which subretinal or vitreous hemorrhage due to birth trauma could still be present), the presence of thrombocytopenia and an emerging vasculopathy due to ROP, it is difficult to ascertain the contribution of the hypofibrinoginemia to the intraocular hemorrhages.

Mansour and Jaroudi (Mansour & Jaroudi, 2012) report the case of a 14 month old male infant born to consanguineous parents. The child presented with unilateral total hyphema and ipsilateral vitreous hemorrhage. There was no evidence to suggest child abuse or accidental trauma, but at this age an unrecognized fall could certainly be possible. Brain computed tomography (CT)

**Table 2**
Findings non specific or indistinguishable from birth hemorrhages*.

| Report | Age | Diagnosis | Eye Findings |
|---|---|---|---|
| *Azar 1974* | < 1 day | Disseminated intravascular coagulation | Hyphema (bilateral)<br>Flame-shaped RH<br>Papilledema |
| *Demir 2015* | 39 weeks | Glanzmann thombasthenia | Retinal "microhemorrhagic areas" (bilateral) |
| *Frankel 1990* | 4 years | Immune thrombocytopenia | VH<br>"small intraretinal hemorrhage" in the posterior pole |
| *Jeronimo 2014* | 29 weeks | Neonatal alloimmune thrombocytopenia | Small perifoveal hemorrhage |
| *Mills 1959* | 3 months | Wiskott-Aldrich syndrome | Hemorrhagic optic nerve border (bilateral) |
| *Totan 1999* | 3 months | Factor V deficiency | "Bleeding Foci" (unilateral)<br>Retinal "edema" (ipsilateral) |
| *Wille 1994* | 1–9 days | Early vitamin K deficiency Bleeding | Scattered RH from peripapillary area to periphery<br>"minor" or "middle-sized" RH<br>Primarily flame-shaped RH |

* Retinal findings are possible in AHT, but nonspecific patterns or <4 weeks old and RH indistinguishable from birth hemorrhages.

**Table 3**
Not enough information*.

| Report | Age | Diagnosis | Eye Findings |
|---|---|---|---|
| *Dale 2002* | "infant" | Neonatal alloimmune thrombocytopenia | Intraretinal RH |
| *Laposta 2005* | 3 months | von Willebrand disease | RH (bilateral) |
| *Lee 2002, Humpl 1999, Shemie 1995, Lane 1983, Goldman 1966, Wetzel 1995* | 3 weeks-2 months | Late Vitamin K deficiency bleeding | RH (unilateral or bilateral) |
| Model, 1977 | 3.5 years | Wiskott-Aldrich syndrome | RH (bilateral) |
| *Rutty 1999* | 9 weeks | Vitamin K Deficiency | RH (bilateral) |

* Detailed retinal findings not provided **or** not enough information to rule out abuse.

**Table 4**
Could potentially be confused for abuse*.

| Report | Age | Diagnosis | Eye Findings |
|---|---|---|---|
| *Botte 2012* | 19 days | Factor VIII deficiency | RH in Posterior pole extending to periphery (unilateral) |
| *Cui 2016* | 7 days | Neonatal polycythemia | Macular hemorrhage and gray retinal folds (unilateral)<br>VH |
| *Curran 1971* | 6 weeks | Factor IX deficiency | Intraretinal hemorrhages (bilateral)<br>Subretinal hemorrhages (bilateral) |
| *Frankel 1990* | 4 years | Idiopathic thrombocytopenic purpura | VH<br>"Small intraretinal hemorrhage" in the posterior pole |
| *Iyengar 2008* | 4 months | Factor XI deficiency | Dense VH (unilateral)<br>Subretinal hemorrhage (ipsilateral) |
| *Levinson 2016* | 8 weeks | Disseminated intravascular coagulation | Intraretinal hemorrhages from the posterior pole to the ora serrata<br>Preretinal hemorrhages (unilateral)<br>Subhyaloid hemorrhage (unilateral) |
| *Marshman 1999* | 36 days | Factor I deficiency | Intraretinal RH (bilateral)<br>Subretinal RH (unilateral)<br>VH (bilateral) |
| *Stray-Pederson 2011* | 11 months | von Willebrand disease | Extensive multilayered RH (bilateral) |

* Reasons confusion for abuse is unlikely: VH is less common in AHT (approx. 11 %),(Bhardwaj et al., 2010), no other systemic signs of abuse (e.g. SDH, fracture), clinical history not suggestive of abuse, or age too young to rule out birth retinal hemorrhage.

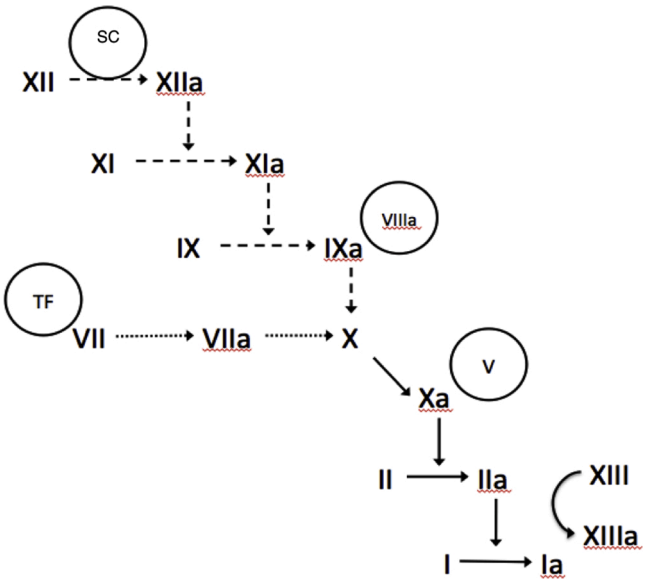


**Fig. 1. The coagulation cascade.** The coagulation cascade is characterized by the intrinsic (denoted with dashed lines) and extrinsic (denoted with doted lines) pathways. The intrinsic pathway is initiated by activation of Factor XII (Hageman factor) by surface contact (SC). The extrinsic pathway begins with the activation of Factor VII by tissue factor (TF). Both the intrinsic and extrinsic pathways physiologically work together to accelerate the production of activated Factor X (Factor Xa). In the presence of Factor V, Factor Xa activates Factor II (prothrombin) to form Factor IIa (thrombin). The coagulation cascade is terminated by thrombin-induced activation of Factor I (fibrinogen) to form Factor Ia (fibrin clot). Incorporation of Factor XIIIa further stabilizes the fibrin clot.

demonstrated a small right epidural hematoma with minimal midline shift. Fibrinogen level was < 0.6 g/L. Despite maintaining fibrinogen levels of 1 g/L by weekly fresh frozen plasma, vitreous hemorrhage recurred after vitrectomy. The appearance of the retina at surgery was not described.

A 3 month old male infant with afibrinogenemia born to consanguineous parents presented with bilateral vitreous hemorrhages and subdural hematomas (Demir, Acar, Aral, & Unlu, 2008). The authors reported no evidence of abuse or trauma. A 14 year old girl was also reported who presented with bilateral subhyaloid hemorrhage. In this case the fibrinogen level was 50 mg/dL (Pathengay, Ambatipudi, & Mehta, 2011).

b) **Factor II (also known as prothrombin).** Prothrombin is an inactive protein synthesized by the liver. Conversion to a potentially active form is vitamin K dependent. In the presence of calcium, Factor Xa forms a prothrombinase complex with Factor Va and phospholipid, which sequentially cleaves prothrombin to its active form, thrombin. Thrombin acts on fibrinogen to form fibrin and contributes to the formation of a stable clot as well as having multiple other functions in the coagulation cascade, such as enhancing clot stability. Prothrombin deficiency is an autosomal recessive disorder with an estimated prevalence of approximately 1 per 1–2 million individuals (Meeks & Abshire, 2008). Affected individuals demonstrate both a prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT). A Factor II assay can be performed if there is a high clinical suspicion for prothrombin deficiency.

Children with prothrombin deficiency may demonstrate a variety of symptoms including hemarthrosis, easy bruising, and mucosal bleeding as well as bleeding precipitated by trauma or surgery (Acharya, Coughlin, Dimichele, North American Rare Bleeding Disorder Study, & G., 2004; Mannucci, Duga, & Peyvandi, 2004; Strijks, Poort, Renier, Gabreels, & Bertina, 1999). intracranial hemorrhage (ICH) was reported in 8% of those homozygous for the disorder and not reported among heterozygotes (Acharya et al., 2004). In the neonatal period prothrombin deficiency may manifest with hematomas, umbilical cord bleeding, or bleeding after circumcision (Marshman et al., 1999; Meeks & Abshire, 2008). Those heterozygous for the disorder are generally asymptomatic, though excessive bleeding has been reported in response to surgery (Girolami et al., 1998; Mannucci et al., 2004).

We are not aware of any reports of children in the AHT age range who were observed to have RH secondary to prothrombin deficiency. RH was not observed in an infant with prothrombin deficiency who presented with intracranial hematoma (Strijks et al., 1999). We are aware of cases in the literature published over 70 years ago of RH reported in adults who were found to have low prothrombin levels but the outdated nature of these reports makes them difficult to interpret (Stewart & Rourke, 1939). There are several case reports of acquired hypoprothrombinemia in children with systemic lupus erythematosus most often accompanied by the presence of lupus anticoagulant. These children did not have RH (Eberhard et al., 1994).

c) **Factor V.** Factor V acts as a plasma cofactor for the prothrombinase complex that activates prothrombin to thrombin. Factor V deficiency may be either congenital or acquired. Congenital Factor V deficiency arises from mutations either in the Factor V gene itself or in the genes that regulate the processing and storage of Factor V. Acquired Factor V deficiency may occur in the setting of rheumatologic disorders, malignancies and antibiotic use, though is relatively less often observed in the pediatric population.

Congenital Factor V deficiency is an autosomal recessive disorder which presents at an early age, with most children presenting with bleeding symptoms prior to 6 years of age (Lak, Sharifian, Peyvandi, & Mannucci, 1998). Factor V activity levels are less than 5% in homozygous patients. Bleeding is most often from mucosal surfaces or post-operative. Hemarthrosis, intramuscular and ICH may also occur.

Perinatal presentation is uncommon. In one cohort, only one patient presented with umbilical stump bleeding (Lak et al., 1998). There are at least seven reports in the literature of perinatal ICH (Ajzner et al., 2002; Chingale, Eisenhut, Gadiraju, & Liesner, 2007; Ehrenforth, Klarmann, Zabel, Scharrer, & Kreuz, 1998; Lee et al., 2001; Salooja, Martin, Khair, Liesner, & Hann, 2000; Totan & Albayrak, 1999; Whitelaw, Haines, Bolsover, & Harris, 1984). Of these, only one report describes RH (Totan & Albayrak, 1999). The other reports fail to state whether an ophthalmic examination occurred. Totan and Albayrak (Totan & Albayrak, 1999) report the case of a 3 month old male infant who had unilateral “bleeding foci” and edema of the retina but no further details were provided. The patient was also found to have a parenchymal hemorrhage with mild edema in the parietal region on CT imaging.

Powers et al. (Powers, Fuchs, & George, 2007) reported a chronic subdural hematoma in a neonate with congenital Factor V deficiency. There was no mention of whether an ophthalmic examination was completed.

d) **Factor VII.** Factor VII is a vitamin K-dependent serine protease whose activation by tissue factor (TF) commences the extrinsic pathway (Fig. 1). The resultant Factor VIIa – TF complex activates Factor IX and Factor X, which subsequently leads to the formation of a stable clot. Even in the absence of activation, a small proportion (1–3 %) of Factor VIIa remains free in circulation. Factor VII deficiency is one of the most common causes of inherited coagulopathy other than hemophilia and von Willebrand disease (VWD), representing 30 % of these disorders (Sevenet, Kaczor, & Depasse, 2017). Diagnosis of Factor VII deficiency is suggested by isolated prolonged PT and confirmed by measurement of Factor VII coagulant activity.

Presentation of congenital Factor VII deficiency is variable. Children most often present with mild bleeding, such as epistaxis (60 %), easy bruising (36 %), and mucosal bleeding, whereas 10–15% may present with serious life- or limb- threatening hemorrhages, including central nervous system (2.5 %), gastrointestinal (15 %) or hemarthrosis (19 %) (Sevenet et al., 2017). Severe bleeding may present soon after birth. ICH may be the presenting symptom in a newborn (Di Minno, Dolce, Mariani, & Group, 2013). Moreover, those children who present with umbilical cord bleeding are reported to have an increased risk for developing severe bleeds at a very young age (Di Minno et al., 2013).

We are not aware of any reports of children in the AHT age range who were observed to have RH secondary to Factor VII deficiency. Punnen et al. (Punnen, Loganathan, Veetiyil, Scott, & Kumar, 2015) describe the case of a 4 day old male neonate diagnosed with congenital proptosis with secondary perforation due to orbital hemorrhage with no ICH. Factor VII activity of the patient was reported to be <1.0 % and enucleation of the eye was performed (Punnen et al., 2015). Proptosis following subgaleal

hematoma after accidental trauma has also been reported in a 6- and a 10-year-old (Jenkins, Zheng, Murchison, & Bilyk, 2017; Pomeranz, Ruttum, & Harris, 1995). There was no mention of RH or vitreous hemorrhage in either patient. Hematological workup revealed Factor VII activity of 37 % (Jenkins et al., 2017) and 46 % (Pomeranz et al., 1995), consistent with heterozygous Factor VII deficiency.

Factor VII deficiency has also been associated in a single case with anterior segment dysgenesis. The 2 month old female born to consanguineous parents presented with seizures secondary to subdural hematoma (Beby et al., 2007). Diagnosis of Factor VII deficiency was made on the third day of life following gastrointestinal bleeding. The anterior segment dysgenesis, with overlap features of Peters anomaly and Axenfeld-Reiger spectrum, may likely have been a coincidental finding. No RH was reported.

Zadok et al. (Zadok et al., 2000) report the case of a 16 year old male, and his mother, who presented with unilateral sub-internal limiting membrane macular hemorrhage in the setting of bilateral retinal arteriolar tortuosity. Factor VII activity was 30 %. His mother had a few unilateral intraretinal hemorrhages but normal coagulation studies. Therefore, it is difficult to attribute the retinal hemorrhage to the Factor VII deficiency as autosomal retinal arteriolar tortuosity is in of itself a known cause of retinal hemorrhage in the second decade of life or later.

e) **Factor VIII (also known as antihemophilic factor A, antihemophilic globulin, or antihemophilic factor).** Factor VIII is a protein that circulates in the bloodstream in an inactive form bound to von Willebrand factor (VWF). In response to injury to blood vessels it separates from VWF and becomes activated. Factor VIIIa then interacts with Factor IX. Factor VIII deficiency is commonly referred to as hemophilia A. Hemophilia A is an X-linked recessive disorder that affects approximately 1 in 6,500 males. The disease is suggested in those with a normal PT and prolonged activated partial thromboplastin time (aPTT) in the context of a normal platelet count. The diagnosis is confirmed upon measurement of low factor VIII clotting activity in the presence of a normal and functional VWF level. The severity of the deficiency can be categorized depending on the Factor VIII clotting activity observed: mild (6 %–40 % clotting activity), moderate (1 %–5 %), or severe (<1%) (Konkle, Huston, & Nakaya Fletcher, 1993).

Children with severe hemophilia A are generally diagnosed in the neonatal period due to birth or neonatal procedure-related bleeding or otherwise during the first year of life. Diagnosis is generally made prior to 6 years of age. Bleeding from minor mouth injuries and hematomas from minor head bumps are the most frequent presenting symptoms in untreated toddlers. Subcutaneous hematomas are also commonly experienced and ICH arising from head injury has been reported (Konkle et al., 1993a; Kulkarni et al., 2009). With growth and increased activity, spontaneous joint and deep muscle hematomas may also occur causing pain and limping before the onset of swelling. Those children with severe hemophilia A who are not treated prophylactically are reported to experience 2–5 episodes of spontaneous bleeding per month. Children with moderate hemophilia A less commonly experience spontaneous bleeding unless in the 1−3% range, although prolonged bleeding after relatively minor trauma may occur. Children with mild hemophilia A rarely experience bleeding episodes though they may experience bleeding with trauma and after surgery or tooth extractions. They are often diagnosed later in life (Konkle et al., 1993a). Heterozygous females whose Factor VIII activity level is less than 40 % are at risk for comparable bleeding as that of males with mild hemophilia A, although bleeding may be variable with Factor VIII clotting activity between 30 % and 60 % (Paroskie, Gailani, DeBaun, & Sidonio, 2015; Plug et al., 2006).

Botte et al. (Botte et al., 2012) report the case of a 19 day old infant who presented in coma. The infant was reported to be pale and apneic with anisocoria and bulging fontanelle. The infant was described to be previously well without a history of trauma. Head CT revealed diffuse subdural hematoma with brain herniation. Funduscopic examination revealed unilateral RH involving the posterior pole and extending to the periphery. Factor VIII activity was less than 5% (Botte et al., 2012). Wang et al. reported a 13 year old boy who presented with visual disturbances and was found to have peripapillary retinal and subretinal hemorrhages unilaterally that resolved 3 months later. Laboratory workup revealed a Factor VIII level of 1.9 % (Wang et al., 2008). There have also been cases of children with hemophilia A with hyphema and subretinal hemorrhage (Aquino & Ranche, 2020) or retrobulbar hemorrhage (Shatnawi, Shweiki, & Khan, 2020) after accidental head trauma. We have seen one case of a 7 day old infant with traumatic birth injury and confirmed hemophilia A. Ocular pathology showed unilateral subretinal hemorrhage in the periphery.

Hemophilia A was noted by Wheeler et al. (Wheeler & Hobbs, 1988) in one case in a retrospective case series of 50 children whose injuries "mimicked" that of non-accidental trauma. The child had bruising that appeared to be "excessive" over his arms, legs and face. There was no comment on whether an eye examination was conducted or the level of Factor VIII activity of the child (Wheeler & Hobbs, 1988). Bray et al. (Bray & Luban, 1987) report three infants who developed ICH and were subsequently diagnosed with hemophilia A. A variety of neuro-ophthalmic signs were seen including "setting sun sign", homonymous hemianopia, and horizontal nystagmus. Retinal examination was reported in one case revealing no papilledema or RH.

f) **Factor IX (also known as Christmas factor).** Factor IX is produced as an inactive zymogen and is vitamin K dependent for activation. When activated by Factor XIa (intrinsic pathway) or Factor VIIIa (extrinsic pathway) in the presence of calcium and phospholipids as well as Factor VIII, it hydrolyses Factor X to Factor Xa. Its action is inhibited by antithrombin. Factor IX deficiency is known as hemophilia B. Diagnosis of hemophilia B is suggested by a normal platelet count, normal PT and prolonged aPTT. Those with mild hemophilia B may have a normal or mildly prolonged aPTT. Diagnosis is confirmed by measurement of Factor IX clotting activity. The Factor IX clotting activity can be used to categorize severity in a pattern similar to hemophilia A (mild, 6 %–40 %, moderate, 1 %–5 %, severe, <1% clotting activity) (Konkle, Huston, & Nakaya Fletcher, 1993). Bleeding manifestations and age of diagnosis are virtually identical to that described above for Factor VIII deficiency (1993b, Konkle et al., 1993a).

Curran et al. (Curran & Wang, 1971) reported a 6 week old male infant with fatal ICH as the first sign of hemophilia B. Four days prior to presentation the mother had reported to have slipped on a staircase while carrying the infant, although direct head trauma to the infant was denied. Bilateral intra- and subretinal hemorrhages were observed. Factor IX activity was 11.5 %. The infant died (Curran & Wang, 1971). Gerlacher et al. (Gerlacher, 1999) reported a 3-month-old with left hemiparesis and a large right cerebral

hemispheric intraparenchymal hemorrhage with midline shift. Funduscopic examination did not reveal RH. Factor IX level was less than 1.7 %. Recurrent hyphema has been reported without RH in a 10 year old child after blunt injury to the eye (Danaee, Patil, Amaya, & Alamelu, 2014) and in a 4 month old infant spontaneously (Ghose, Kishore, Patil, & Saxena, 1993). Spontaneous orbital hemorrhage has also been reported (Teke, Akay, Gunduz, Tokmak, & Saylisoy, 2013). Hemophilia B was confused with non-accidental trauma in 8 (Harley, 1997) and 10 month old infants (Schwer, Brueschke, & Dent, 1982). The former had extensive bruising while the latter had an incidental healing clavicle fracture not attributable to the hemophilia. No comment was made as to whether an eye examination was conducted in either of these children (Harley, 1997; Schwer et al., 1982).

g) **Factor X.** Factor X is a vitamin K-dependent plasma glycoprotein. It is the first enzyme in the common pathway leading to the formation of thrombin. Factor X deficiency is rare among the inherited coagulopathies and represents approximately 10 % of these disorders (Menegatti & Peyvandi, 2009; Uprichard & Perry, 2002). Approximately 1 in 1,000,000 individuals are affected (Menegatti & Peyvandi, 2009; Uprichard & Perry, 2002). Diagnosis of Factor X deficiency is suggested by concomitant prolongation of the PT and aPTT time and confirmed by measurement of Factor X activity.

Of those patients with inherited coagulopathies, patients affected by Factor X deficiency tend to be among those most seriously affected. Bleeding tendency may present at any age. While epistaxis is the most common symptom, those most seriously affected (Factor X activity <1%) may develop umbilical cord or CNS bleeding early in life (Menegatti & Peyvandi, 2009; Uprichard & Perry, 2002). ICH has been described with this deficiency with a high propensity in those with a Gly380Arg mutation in the F10 gene (Herrmann et al., 2006). Children with severe Factor X deficiency may also experience hemarthrosis, subcutaneous hematomas, and hematuria. Those children less seriously affected may only bleed after trauma or surgery (Factor X activity 1 %–5 %). Some cases may be asymptomatic or have epistaxis and are identified solely during routine screening or genetic studies (Factor X activity 6 %–10 %) (Menegatti & Peyvandi, 2009; Peyvandi et al., 1998; Uprichard & Perry, 2002).

Sumer et al. (Sumer, Ahmad, Sumer, & Al-Mouzan, 1986) report a one year old boy with homozygous Factor X deficiency. During a hospital admission for rectal bleeding he became unresponsive. Brain CT revealed subarachnoid bleeding extending to the occipital lobes. Ophthalmic examination was not described. The child later was found to have cortical visual impairment. Shim et al. report an infant with multiple spontaneous ICH. An ophthalmologist followed the infant for eye motility abnormalities following his second ICH episode. More details of the ophthalmic examination were not provided. In large series reporting the clinical manifestations of Factor X deficiency there have been no mention of ophthalmic examinations (Herrmann et al., 2006; Peyvandi et al., 1998). To the best of our knowledge there are no reports of RH in this disease.

h) **Factor XI (also known as antihemophilic factor C).** Factor XI is a serine protease zymogen whose activation by Factor XIIa, thrombin or autocatalysis leads to the cleavage of Factor IX. Factor XI deficiency may be referred to as hemophilia C or Rosenthal syndrome. Factor XI deficiency affects approximately 1 in 1,000,000 individuals though its frequency is reported to be approximately 1 in 450 individuals of Ashkenazi Jewish decent (Duga & Salomon, 2013). It may be considered in those with a prolonged aPTT in the context of a normal PT after hemophilia A and hemophilia B have been ruled out, although lupus anticoagulant and Factor XII deficiency may also alternatively explain such laboratory findings. Measurement of Factor XI activity provides confirmation of diagnosis.

Diagnosis of Factor XI deficiency is rarely made because of spontaneous bleeding. Bleeding manifestations in children with severe Factor XI deficiency (<20 IU/dL) are most often injury-related and correlated with the site of injury (Duga & Salomon, 2009). However, bleeding cannot be predicted by the factor level. The risk of bleeding is increased (49–67 %) in sites of injury with high fibrinolysis (oropharynx and genitourinary tract) as compared to those sites without fibrinolysis (1.5 %–40 %) as Factor XI indirectly increases thrombin-activatable fibrinolysis inhibitors, which reduces fibrinolysis and leads to better stabilized clot formation (Duga & Salomon, 2009).

We are not aware of any cases of RH in children with Factor XI deficiency other than Iyengar et al. (Iyengar, Olitsky, & Neville, 2008) who reported a 9-month-old who developed dense vitreous and subretinal hemorrhage following congenital cataract extraction with anterior vitrectomy. Factor XI activity was reported to be decreased though no comment was provided as to its level. Prior to congenital cataract extraction in the second eye, the infant was transfused with fresh frozen plasma to elevate his Factor XI levels above 40 % as well as administered a 10-day course of ε-aminocaproic acid to maximize clot stabilization. Vitreous hemorrhage still occurred in the fellow eye oneweek postoperatively though it was reported to resolve spontaneously at one month follow-up (Iyengar et al., 2008).

i) **Factor XII.** Factor XII is a plasma protease which binds to negatively charged surfaces and activates the contact system. Factor XII deficiency leads to a prolonged aPTT. Factor XII levels have broad reference ranges and vary with age and ethnicity (Han et al., 2015). Factor XII deficiency is not a bleeding disorder. Affected individuals, even with severe Factor XII deficiency, do not suffer from spontaneous- or injury-related bleeding (Renne & Gailani, 2007). This intact homeostasis has led to the hypothesis that this pathway may be dispensable during bleeding, with fibrin formation being solely dependent on the extrinsic pathway. Although Factor XII deficiency is not associated with bleeding tendency, thromboembolic events may occur despite a prolonged aPTT (Renne & Gailani, 2007). The relationship between thrombosis and Factor XII deficiency is often cited but unproven (Han et al., 2015). We are not aware of any reports of RH other than adults with RH secondary to central or branch retinal vein occlusions (Borrego-Sanz et al., 2014; Kuhli, Scharrer, Koch, Ohrloff, & Hattenbach, 2004).

j) **Factor XIII (also known as Fibrin stabilizing factor).** Factor XIII is a pro-enzyme, which cross-links fibrin and facilitates clot stability. The estimated prevalence is 1 in 2,000,000 individuals (Dorgalaleh, Tabibian et al., 2016). with approximately one third occurring due to consanguineous cases in Iran (Dorgalaleh, Naderi, & Shamsizadeh, 2016). This disorder may be under diagnosed as routine coagulation tests have normal findings (Dorgalaleh, Tabibian et al., 2016). Factor XIII activity level, antigen assays, and/or gene sequencing are required to confirm the diagnosis (Dorgalaleh, Tabibian et al., 2016).

Infants with Factor XIII deficiency may experience umbilical cord bleeding (>80 %) and increased bruising (Dorgalaleh, Tabibian et al., 2016). There is a particularly high risk of spontaneous ICH (approximately 33 %) in the first two decades of life (Dorgalaleh, Naderi et al., 2016). The most common site for ICH in Factor XIII deficiency is intraparenchymal. Subdural hemorrhage (SDH) is notably rare (Naderi et al., 2014). Early diagnosis and treatment are essential to prevent life-threatening bleeds. Factor XIII also serves several important functions in angiogenesis, wound healing, and maintenance of pregnancy (Dorgalaleh, Tabibian et al., 2016). To the best of our knowledge RH has not been reported in Factor XIII deficiency. Larsen et al. reported an infant with severe Factor XIII deficiency including two spontaneous (non-traumatic) episodes of ICH. Ophthalmic consultation did not show RH (Larsen, Wallace, Frankel, & Crisp, 1990).

k) **von Willebrand disease.** e VWD is due to a deficiency or dysfunction of the VWF glycoprotein. It is the most common inherited bleeding disorder. The role of the protein in hemostasis is to stabilize Factor VIII in circulation and mediate platelet adhesion and aggregation at sites of vascular injury (Lillicrap, 2013). The current prevalence of VWD is difficult to describe due to changing diagnostic criteria, but the estimate is between 1 in 100 to 10,000 (Lillicrap, 2013). The phenotype is heterogeneous with common symptoms including easy bruising, prolonged mucosal and skin bleeding, and heavy menstruation. The diagnosis of VWD can be challenging at times, as some patients with low von Willebrand (VW) antigen and/or VW activity may not have bleeding symptoms. Additionally, VWF is an acute phase reactant, increasing in episodes of illness thus further complicating diagnosis. Most recent National Heart Lung and Blood Institute guidelines define the diagnosis of VWD as having a VWF antigen or activity < 30 %. Factor VIII activity may also be low. Type 1 and 3 VWD are quantitative deficiencies of the VWF, while the various type 2 subtypes are caused by a dysfunctional VWF molecule (Nichols et al., 2009). Subtypes of VWD that influence Factor VIII more profoundly may have manifestations similar to hemophilia, such as joint and soft tissue bleeding.

To our knowledge there have been few reports of ophthalmic manifestations worldwide (Laposata et al., 2005; Lin & Chang, 2016; Stray-Pedersen, Omland, Nedregaard, Klevberg, & Rognum, 2011). Herrmann et al. report a 33 year old man with spontaneous “blurred and spotted vision”. Ophthalmic exam revealed subhyaloid, intraretinal, and subretinal hemorrhages. RH were scattered and few in number (Herrmann, Lohmann, Demmler-Hackenberg, & Gabel, 2005). Shiono et al. (Shiono et al., 1992) report a 13 year old Japanese girl whose first presentation of VWD was unilateral “spotted vision” with a best corrected visual acuity of 20/30 in the symptomatic eye. Ophthalmic examination revealed peripapillary retinal and subretinal hemorrhages, as well as vitreous hemorrhage. Although not mentioned by the authors, there also appears to be subinternal limiting membrane hemorrhage in the macula without a perimacular fold. Systemic examination and brain CT scan were normal. There was no history of trauma. Coagulopathy work-up revealed a decreased Factor VIII (51 %) and decreased VWF (55 %), however, this does not meet diagnostic criteria for VWD. In 2011, Stray-Pedersen et al. (Stray-Pedersen et al., 2011) presented an 11 month old girl with subdural hematoma and extensive multilayered bilateral RH which developed after reportedly falling backward from standing and hitting her head on a carpeted wooden floor. On hospital admission, coagulation tests were unremarkable and there were no signs of external trauma. Six months following her hospitalization, repeat evaluation was felt to be consistent with VWD (FVIII 48 %, VWF:AG 33 %), though this does not meet current diagnostic criteria. Note that occipital impact may in of itself be a risk factor for RH (Atkinson, van Rijn, & Starling, 2018). Laposata & Laposata (Laposata & Laposata, 2005) describe two cases of children they felt had VWD. A 3 month old infant presented with seizures, bilateral RH (no details given), and subdural and subarachnoid hematoma after the father sharply pulled the child up from a fall before impact was made. Evaluation for bleeding disorders were unrevealing. Due to suspicion of child abuse, the child was placed in foster care during which three months later the child was hospitalized for meningitis and a subdural hematoma. Repeat evaluation thereafter was felt to be consistent with “moderately severe” VWD (lab values not given). A 1 year old child who reportedly fell a few feet headfirst onto a hardwood floor developed a SDH and bilateral RH (no details given). Initial hospital evaluation for bleeding disorders did not include VWD. Six months after the injury took place, the child and two siblings were diagnosed with VWD (lab values not given). In a study describing a cohort of 500 individuals with VWD in Sweden, there were three reports of “eye bleeding” without further details (Silwer, 1973). Although the individual ages of these cases are not given, the youngest individual in the total cohort was 2 years old.

### 3.2. *Vitamin K deficiency*

Vitamin K has an important function in normal hemostasis as its role as a cofactor in carboxylation is essential for the production of prothrombin, Factor VII, IX, X, protein C and protein S. (Vermeer, 1985) It is a fat soluble vitamin that is typically obtained through the diet as well as synthesized by the gastrointestinal flora.(Harshman, Saltzman, & Booth, 2014) Newborns are particularly susceptible to vitamin K deficiency as the fat-soluble vitamin poorly transfers across the placenta, resulting in low hepatic stores at birth. Newborns also lack much of the vitamin producing gastrointestinal flora (Carpenter, Abshire, & Anderst, 2013). Breast milk is a poor source of vitamin K as compared to cow’s milk and infants who are exclusively breastfed are at increased risk of vitamin K deficiency bleeding. (Motohara et al., 1984) Infants with severe deficiency of vitamin K may develop life-threatening bleeding. Therefore, neonatal vitamin K supplementation has become standard in most countries (Carpenter, Abshire, Anderst et al., 2013).

There are three types of vitamin K deficiency bleeding (VKDB). Early VKDB is usually seen within the first 24 hours of life and is associated with maternal medications that interfere with vitamin K absorption, classic VKDB occurs within the first two to four weeks of life and is associated with poor or delayed oral intake, and late VKDB is seen thereafter in infants who are exclusively breastfed without supplementation or with biliary obstruction. The most common clinical findings are bruising and gastrointestinal bleeding. Late VKDB carries a significant risk for severe ICH (Shearer, 2009).

There have been a number of reports that describe RH in the setting of early (Ratageri, Shepur, & Kiran, 2007; Wille, 1944), classic (Thapa, Biswas, & Mallick, 2011) and late (Humpl et al., 1999; Lane, Hathaway, Githens, Krugman, & Rosenberg, 1983; Lee, Li, & So,

2002; Shemie & Cutz, 1995) VKDB. In 1994 Wille was the first to suggest that vitamin K deficiency may contribute to birth-related RH (Wille, 1944). In a series of 910 newborns, the rate of birth-related RH observed was lower in those whose mothers received vitamin K treatment (31.0% versus 42.4%). RH were most commonly intraretinal and preretinal and resolved within two weeks. Less commonly, RH was seen across the entire retina including the periphery. Ophthalmic findings secondary to classic VKDB are much less common. In 2011 Thapa et al. reported a 6-day-old delivered by vaginal delivery who developed pallor along with dark stool and urine. The patient was only breastfed and did not receive vitamin K supplementation. Examination by ultrasound revealed bilateral vitreous hemorrhage that resolved within 10 days (Thapa et al., 2011). In late VKDB, RH is more commonly seen and, to our knowledge, have only been reported in those that were exclusively breastfed (Chaou, Chou, & Eitzman, 1984; Goldman & Deposito, 1966; Humpl et al., 1999; Lane et al., 1983; Lee et al., 2002; Shemie & Cutz, 1995; Wetzel, Slater, & Dover, 1995). Details of the type, location and number of RH are rarely given. RH were either unilateral or bilateral, but no other details were given. One of the author's (AVL) examined the child reported by Shemie and Cutz, finding only few intraretinal hemorrhages in the posterior pole of one eye. Two cases have been reported of infants with subdural hemorrhage and RH that were attributed to vitamin K deficiency, but abuse was not ruled out. Both infants presented unresponsive (Rutty, Smith, & Malia, 1999; Tarau, Wang, Nentwich, Hillenkamp, & Kampik, 2019). RH were detailed in one of the articles as intraretinal and preretinal with white centers (Tarau et al., 2019).

### 3.3. Platelet function abnormalities

Platelet function is an integral part of normal hemostasis. The platelet plug provides a basis for initial hemostatic control and later supports the role of coagulation factors. The formation of the platelet plug is complex but may be distilled into a few major processes: platelet adherence, activation, and aggregation.

Platelet function abnormalities may be acquired or inherited. Common causes of acquired dysfunction include liver disease, uremia, myeloproliferative disease, or trauma. Although each inherited disorder of platelet function is rare, the multitude of varied causes together are a significant cause of inherited bleeding diatheses. While family history and syndromic presentations may help, diagnosis remains a challenge, often first relying on the exclusion of acquired causes (Gresele, Falcinelli, & Bury, 2018). Standardized assessment tools have been developed to assist in identifying patients but have yet to be validated (Gresele et al., 2018). Inherited disorders may present with unique symptoms, although like the acquired causes, most commonly present with postsurgical, traumatic, and/or mucocutaneous bleeding (Gresele et al., 2018). Muscle hematomas, CNS bleeding, and gastrointestinal bleeding are less commonly seen (Gresele et al., 2018).

Some of the inherited platelet function disorders may have associated findings that prompt ophthalmic evaluation, such as nystagmus due to albinism in Hermansky-Pudlak syndrome (Peters & Grainger, 2017). In 2000 Rusell-Eggit et al. (Russell-Eggitt, Thompson, Khair, Liesner, & Hann, 2000) reported a case of an infant with spontaneous RH diagnosed with Hermansky-Pudlak syndrome. This infant had a number of bleeding episodes before the RH were recognized including a cephalohematoma from forceps delivery, epistaxis, and a subdural hematoma. The RH were restricted to the posterior pole and asymmetric with a single hemorrhage in the left macula and the right eye showing a dozen subhyaloid, intraretinal, and subretinal hemorrhages. To our knowledge there are no other reported cases of RH in the syndromic platelet dysfunction disorders.

Glanzmann thrombasthenia (GT) is an autosomal recessive disorder of platelet aggregation commonly presenting during infancy and early childhood (Demir, Kaba, Garipardic, Peker, & Tuncer, 2015; Kamburoglu & Kiratli, 2006; Kannan & Saxena, 2017; Kannan et al., 2009; Saatci et al., 2002; Walsh, 1972). The 2002 report by Saatci et al. (Saatci et al., 2002) describes an 11 year old girl who developed bilateral vision loss two days after a blood transfusion and hospitalization for fatigue, pallor, and petechiae. Ultrasound showed bilateral choroidal hemorrhages. At the one month follow-up, the choroidal hemorrhages were resolving but intravitreal hemorrhage with tractional retinal detachment was observed bilaterally. Demir et al (Demir et al., 2015) describe a newborn girl whose twin died in utero. At birth, wide-spread ecchymotic skin lesions and weak neonatal reflexes were noted, which raised suspicion for early sepsis. The infant received antibiotic therapy in an intensive care unit, and with resolution of the skin lesions, was discharged after five days. One week following the discharge, the disseminated ecchymosis returned and retinal "microhemorrhagic areas" were noted in both eyes. She was subsequently found to have GT based on platelet aggregation studies. In a series of patients with GT, Walsh et al. (Walsh, 1972) described a 5 year old girl who throughout her life experienced multiple hospitalizations due to severe epistaxis, spontaneous gingival bleeding, bleeding after the loss of her deciduous teeth, and severe bruising. At eight different bleeding episodes she required blood transfusions, platelet transfusions, and cryoprecipitate. At birth she was diagnosed with vitamin K deficiency, and at one year old was diagnosed with VWD. Following a hospitalization for treatment of a severe bleeding episode, severe bilateral vitreous hemorrhages were noted. In a series of 45 patients with GT, Kannan et al. (Kannan & Saxena, 2017; Kannan et al., 2009) describe four patients with ocular bleeding. Two of these four patients were 11 and 14 year old boys, both of whom had many other bleeding events requiring blood transfusions including epistaxis, ecchymosis, and gastrointestinal bleeding. The other two children were not described further. A 12 year old child with recurrent traumatic hyphemas and GT was described by Kamburoglu et al. (Kamburoglu & Kiratli, 2006) In this report, the child experienced three episodes of total hyphema, each a year apart following a range of injuries.

Wiskott-Aldrich syndrome (WAS) is an X-linked immunologic disorder classically characterized by eczema, recurrent infections, and thrombocytopenia with dysfunction of platelet aggregation. The ophthalmic manifestations seen in this disorder have been well described by Podos et al. in 1969 (Podos, Einaugler, Albert, & Blaese, 1969). Serious, recurrent viral and bacterial infections of the conjunctiva and eyelids are described in children with WAS. One almost 3 year old child with recurrent bleeding episodes and infections requiring hospitalization was noted to have bilateral vitreous hemorrhages (Root & Speicher, 1963). A 3 month old child with WAS, symptomatic with eczema, petechiae, and ecchymoses, was admitted for a platelet transfusion. Ophthalmic examination showed

hemorrhagic borders to one optic nerve (Mills & Winkelmann, 1959). In 1977, Model (Model, 1977) reported a boy with WAS who required multiple admissions for treatment of infected eczema, thrombocytopenia, epistaxis, gastroenteritis, and weight loss. When the child was 3 years old, he presented to the hospital with multiple neurologic deficits and a petechial rash. Ophthalmic examination revealed "bilateral RH". Further work-up revealed three brain reticulum cell sarcoma lesions. A 3-year-old with platelet factor 3 defect presented with a rapid decrease in vision and was found to have bilateral vitreous hemorrhage. Skeletal survey and neuroimaging were not done (Naithani, Mehrotra, Venkatesh, Wadhwa, & Garg, 2008).

### 3.4. Thrombocytopenia

Thrombocytopenia is most commonly defined as a platelet count below $150 \times 10^9$/L (Balduini & Noris, 2015). In the absence of a concurrent platelet function abnormality, the risk for non-spontaneous bleeding increases as platelet counts fall below $100 \times 10^9$/L (Balduini & Noris, 2015). Spontaneous bleeding may be observed at platelet counts below $50 \times 10^9$/L, and the risk continues to increase as platelet counts fall below $20 \times 10^9$/L (Balduini & Noris, 2015).

Thrombocytopenia in the pediatric population has a wide range of inherited and acquired etiologies. The inherited thrombocytopenias alone are a heterogeneous group of disorders that have great variability in their presentation, with 33 unique forms currently identified (Balduini & Noris, 2015; Noris & Pecci, 2017). Between 18–25% of all neonatal intensive care unit admissions are complicated by thrombocytopenia with a rate in neonates of 1.8 in 1000 live births (Resch, Hinkas, Urlesberger, & Resch, 2018).

In addition to their hemostatic role, platelets may influence angiogenesis through their role in transporting and releasing growth factors such as vascular endothelial growth factor and insulin-like growth factor-1 (Italiano et al., 2008; Smyth et al., 2009). Longitudinal studies have confirmed a relationship between thrombocytopenia and the development and severity of ROP (Cakir et al., 2018; De Alba Campomanes, Jensen, Ying, Tomlinson, & Binenbaum, 2018; Jensen, Ying, Huang, Quinn, & Binenbaum, 2018; Sancak, Toptan, Gokmen Yildirim, Karatekin, & Ovali, 2019). In rare cases, thrombocytopenia has been identified in neonates as part of an evaluation for subconjunctival or vitreous hemorrhage during routine ROP screening (Chandra, Kumawat, Kumar, & Tewari, 2017; Funnell & Simmons, 2008).

Despite the frequency of thrombocytopenia in pediatric patients, ophthalmic bleeding as a presenting sign of low platelet counts is not common and difficult to attribute to thrombocytopenia alone. We are aware of two cases in which immune thrombocytopenic purpura (ITP) was implicated in causing retinal and vitreous hemorrhage (accompanied by ICH) in a child (Frankel & Pastore, 1990), and RH, without further description, in a teenager (Tantawy et al., 2020). Even in ITP, thrombocytopenia may not be the lone risk factor for RH. The antibodies targeting platelet surface glycoproteins may also react with the endothelium of blood vessels (Levine, Adams, Silver, & Fernandez-Rocha, 1976) and have been proposed to be the cause of retinal exudates in affected adults (Goel, Arora, Jain, & Ghosh, 2014). Indeed, even severe thrombocytopenia in adults rarely results in RH in isolation. In their 1968 case series of adults with thrombocytopenia, anemia, or both, Rubenstein et al. identified RH only in those subjects whose thrombocytopenia was accompanied by anemia (Rubenstein, Yanoff, & Albert, 1968). A retrospective case series of 75 children ages 0.5–16 years with ITP, in which fundus examination was done on 61 (79 %) RH was ruled out in all cases and the only remarkable finding was optic neuropathy (Capua et al., 2019). RH are present in a variety of pediatric case reports of scenarios accompanied by thrombocytopenia including macular hemorrhage in polycythemia (Cui, Zhang, Liang, Li, & Hao, 2017), intraretinal hemorrhage in neonatal alloimmune thrombocytopenia (Dale & Coleman, 2002; Jeronimo, Azenha, Mesquita, & Pereira, 2014), bilateral dot and blot, peripapillary flame-shaped, intraretinal, and premacular RH in hemolytic uremic syndrome (Geraissate, Yamamoto, Isaac, & Avila, 2014; Sturm, Menke, Landau, Laube, & Neuhaus, 2010; Zheng et al., 2014), preretinal and subretinal hemorrhages confined to the posterior pole in systemic lupus erythematosus (Zhang, Chen, Yu, & Liu, 2018) and preretinal, few in number RH confined to the posterior pole in aplastic anemia (Mansour et al., 2014). Vitreous hemorrhage with thrombocytopenia has been described in cases of hemolytic uremic syndrome (Sandhu & Vavvas, 2015). Vitreous hemorrhage, and unilateral subretinal hemorrhages with vessel sclerosis have been reported in dyskeratosis congenita with thrombocytopenia (Finzi, Morara, Pichi, Veronese, & Ciardella, 2014; Moussa, Huang, & Moore, 2017). Hyphema was reported in one case of neonatal alloimmune thrombocytopenia (Jeronimo et al., 2014). In their 1995 evaluation of RH and extracorporeal membrane oxygenation (ECMO), Pollack and Tychsen were not able to associate differing platelet counts during ECMO with the development RH (Pollack & Tychsen, 1996). In their 2005 study Simon et al. identified cases in which thrombocytopenia was believed to be the most common non-idiopathic etiology of vitreous hemorrhage warranting vitrectomy (Simon et al., 2005). A poll sent to the American Association for Pediatric Ophthalmology and Strabismus ListServe provided reported etiologies of vitreous hemorrhage. From 21 cases, listed causes included 9 unknown, 5 thrombocytopenia, 4 child abuse, 1 birth trauma, and 1 hypertension. The poll results excluded additional patient history, making the data insufficient to conclude that the vitreous hemorrhage was due to thrombocytopenia alone.

### 3.5. Disseminated intravascular coagulation (DIC)

In disseminated intravascular coagulation (DIC), there is systemic activation of coagulation resulting in widespread bleeding and consumption of thrombin in small and medium sized blood vessels (Wada, Matsumoto, & Yamashita, 2014). There are many potential causes of DIC including infection, solid and hematologic malignancies, trauma, liver disease, vascular abnormalities and others (Levi, Toh, Thachil, & Watson, 2009). The manifestations of DIC can be divided into four broad categories: asymptomatic, organ failure, bleeding, and massive bleeding (Wada et al., 2014). DIC may be due to a predominately prothrombotic presentation, as is more common in sepsis, or a predominately fibrinolytic presentation. Thrombosis or bleeding may result in either scenario, which is also a common presentation of DIC in acute promyelocytic leukemia. Consumptive coagulopathy with massive bleeding may occur

(Rajagopal, Thachil, & Monagle, 2017). The diagnosis of DIC is made by laboratory testing interpreted in the context of the clinical setting. A number of scoring systems have been proposed, for example, the International Society on Thrombosis and Haemostasis incorporates platelet count, fibrin-related markers, PT, and fibrinogen levels in their scoring system (Taylor et al., 2001).

Intraocular bleeding in the pediatric population with DIC has been reported. The variety of ophthalmic findings may reflect the diverse etiologies and/or severities of DIC. In newborns with DIC associated with respiratory distress syndrome, RH was unilateral or associated with extraretinal bleeding such as vitreous hemorrhage or hyphema (Azar, Smith, & Greenberg, 1974; Wiznia & Price, 1976). In 2002 Dinakaran et al. prospectively studied retinal involvement in 12 children with DIC due to meningococcal septicemia (Dinakaran, Chan, Rogers, & Brosnahan, 2002). Flame-shaped and dot/blot RH were observed in 5 children and were characterized as bilateral, predominately posterior to the equator, scattered, and numbering less than 20. The authors note that these findings contrasted with those seen in non-accidental trauma. In the children who survived, follow-up examinations at 9–12 months disclosed normal appearing fundi. Other cases similarly had RH predominately posterior to the equator, but were accompanied by iris hemorrhage, vitreous hemorrhage, subconjunctival hemorrhage, and/or subdural and subarachnoid hemorrhage of the optic nerve sheath. Viola et al. reported a case of a 5 year old female with severe nephrotic syndrome who subsequently developed DIC. Fundus examination showed bilateral ischemic retinal whitening and a single RH over the fovea of the left eye, which resolved after 3 weeks (Viola et al., 2013). In a case report by Levinson et al., bilateral intraretinal hemorrhages that extended to the ora serrata and hypoxic ischemic brain injury in an 8 week old infant was attributed to DIC. Abuse was ruled out based on investigations by the police and medical examiner, but the Child Protection Team maintained suspicion for abuse. Full medical workup for child abuse was not done. The authors write, "In a case such as this, it may be difficult to determine whether abuse led to myocardial infarction and subsequent coagulopathy or whether the infant suffered an infarct and then developed signs of cerebral hypoxia and retinal hemorrhages as a result of complications of the infarct and its treatment" (Levinson, Pasquale, & Lambert, 2016).

### 3.6. *Traumatic brain injury-associated coagulopathy*

Trauma induced coagulopathy (TIC) can often follow traumatic brain injury (TBI) (Kushimoto, Daisuke, & Kawazoe, 2017; Maegele et al., 2017). TIC from TBI has a pathophysiology distinct from DIC. Brain tissue is rich in pro-coagulant molecules that are released into the blood in the setting of parenchymal injury (Zhang et al., 2012). This process, believed to be driven primarily by tissue factor, activates hemostatic systems, which induces a consumptive coagulopathy and “platelet exhaustion” (Chang, Cardenas, Wade, & Holcomb, 2016; Zhang et al., 2012). Other aspects of the pathophysiology are still under investigation. Patients present with variable degrees of prolonged PT and aPTT, elevated international normalized ratio (INR), and thrombocytopenia. In 2017, Maegele et al. conducted a literature review on the prevalence of coagulopathy in TBI in both adults and children. Sixteen of the studies reported cutoff values to define coagulopathy. Of those 16, eight included specific ranges of aPTT, INR, and platelets for TIC patients. Mean value ranges for aPTT, INR, and platelets were 25–56.3 s, 1.1–2.1, and 80,000–256,000 platelets per L, respectively. Highest reported values overall for aPTT and INR were 85.4 s and 2.3, respectively. Lowest reported value for platelets was 75,000 platelets/$mm^3$ (Maegele et al., 2017).

In a meta-analysis by Harhangi et al. in 2008, about one third of pediatric patients with moderate to severe TBI developed coagulopathy, as compared to less than 1 % with mild TBI (Harhangi, Kompanje, Leebeek, & Maas, 2008). Patients with TIC as a result of TBI have increased mortality and worse clinical outcomes (Harhangi et al., 2008; Hendrickson et al., 2012; Leeper, Nasr, McKenna, Berger, & Gaines, 2016; Whittaker et al., 2013). Drastic changes in laboratory values (PT, aPTT, INR) are rare and have a strong association with more severe injury (Hollingworth et al., 2007; Talving et al., 2009).

In 2009, Talving et al. reviewed 302 cases of TBI in patients under 18 years old of which less than half (42 %) developed coagulopathy. Approximately 75 % had an INR value below 1.6, a PTT less than 46 s, and a platelet count above 80,000. Patients within the AHT age range had a lower incidence of coagulopathy than adolescents (26.0 % versus 50.7 %). More severe coagulopathy was associated with more severe injuries as defined by lower Glascow Coma Scale (GCS) and increased intraparenchymal contusions and lacerations (Talving et al., 2009). In another retrospective review of coagulopathy in TBI patients under 16 years old, average PT, PTT, and INR in patients with CTs that showed evidence of intracranial injury were 18.03 (+/− 9.96), 12.5 (+/- 18.12), and 2.17 (+/− 2.28), respectively. Maximum values or any comments on extreme outliers were not provided (Keller, Fendya, & Weber, 2001). Hymel et al. compared coagulopathy values in child victims of AHT with and without parenchymal damage. Subjects with parenchymal damage were more likely to have changes in PT (median 13.1 s, 5th to 95th percentile range 11.2–18.1), aPTT (median 30.2 s, 5th to 95th percentile range 21.1–63.4), and platelets (median 411,000/$mm^3$, 5th to 95th percentile range 199,000–278,000). Although these values overlap with the normal range, PT prolongations and activated coagulation were more commonly found in children with evidence of parenchymal injury on imaging. Outliers included PT and aPTT values of 33.3 s and 151.3 s, respectively, and a platelet count of 55,000 (Hymel, Rumack, Hay, Strain, & Jenny, 1997). In another study, only 6% of children with TBI had markedly abnormal coagulation studies, and these were associated with additional clinical manifestations of severe trauma (GCS $< 13$, low systolic blood pressure, open/multiple bony fractures) (Holmes, Goodwin, Land, & Kuppermann, 2001). To our knowledge, there have been no studies documenting RH findings specifically due to TIC from TBI. The majority of cases present with mild to moderate elevations in coagulation profiles, and of those cases with severe elevations, evidence of major trauma (intraparenchymal injury, low GCS, multiple fractures) was present, which may in of itself be expected to account for RH and could also distinguish between accidental and abusive trauma if there is an obvious history (Holmes et al., 2001; Hymel et al., 1997; Keller et al., 2001; Talving et al., 2009). Other disorders with similar coagulopathy severity, as shown in this review, seem not to be associated with severe RH, retinal folds or retinoschisis. Therefore, we may extrapolate to suggest that these findings would suggest abuse.

## 4. Conclusions

Disorders of coagulopathy rarely result in RH in children. RH has not been reported in congenital Factor II, VII, X, XII, or XIII deficiencies. In the vast majority of cases where coagulopathy occurs in a child with RH, the etiology can be identified by history, family history, or other findings on ocular and physical examination as well as laboratory studies. Many of the reports of coagulopathy with RH clearly raise no concerns for abuse, for example, because the child falls outside the typical age range for AHT, the absence of other indicators of abuse on physical or ocular history or exam, or there are other systemic or ocular findings that have not been reported in AHT and help to identify the coagulopathy. Deficiencies of Factors V, VIII, and IX as well as VWD have reported cases in which ICH and RH were present and the initial underlying disorder was not obvious. AHT was considered in these cases, but ocular findings more diagnostic of AHT, such as retinoschisis or paramacular retinal folds, were absent and there were no other indicators of abuse. In some reports, it is difficult to assess the degree to which RH might mimic AHT as there may be no further eye details reported (Chaou et al., 1984; Goldman & Deposito, 1966; Humpl et al., 1999; Lane et al., 1983; Lee et al., 2002; Shemie & Cutz, 1995; R.C. Wetzel et al., 1995). In one case of Factor V deficiency, eye findings were described as "bleeding foci" and retinal "edema" with no other details reported (Totan & Albayrak, 1999). Although any degree of RH can be seen in AHT, milder RH are less specific for AHT (Levin, 2010). More extensive RH has been reported in hemophilia A and B, with RH extending to the periphery and intraretinal and subretinal hemorrhages, respectively (Botte et al., 2012; Curran & Wang, 1971). Extensive, multilayered RH has been reported in mild VWD (Stray-Pedersen et al., 2011). None of these cases presented with key characteristics of RH in AHT, such as retinoschisis or perimacular folds. Also, two of these cases presented with the history of head trauma from a fall (Curran & Wang, 1971; Stray-Pedersen et al., 2011), which may have intensified the retinal appearance in the presence of coagulopathy.

Our review suggests that any RH is rare in coagulopathies and even when present, rarely show the severity seen in two thirds of AHT (Levin, 2010). Our review does have several limitations. Not all cases of RH in coagulopathies are reported as ophthalmology consultation is not routine in children with coagulopathies, even when there is head trauma. It is possible that more cases, even those with more significant RH, could be revealed if such systematic examination was conducted. Similarly, there were cases reported that did not include full evaluation by a hematologist to confirm or dispute the coagulopathy diagnosis. Younger children can have significant retinopathy without any symptoms. Reported cases outside the AHT age range were not included, but there is no way to exclude the possibility that manifestations that happen in older children can happen in younger children as well. It is also difficult to "prove the negative". Even with a zero incidence over 100 patients, there is still up to a 3% chance that the observation could be missed by chance (Hanley & Lippman-Hand, 1983). The effect of multiple factors (e.g. coagulopathy with AHT and other significant medical sequelae) is impossible to assess in a review such as this. Severe hemorrhagic retinopathy is rare in children with critical illnesses, and often the hemorrhagic retinopathy is readily attributed to diagnoses other than AHT, such as motor vehicle crashes (Agrawal, Peters, Adams, & Pierce, 2012). It is difficult to determine whether the coagulopathy served as a primary cause or contributor to ocular manifestations in cases where both coagulopathy and trauma were present. In one particular case, extensive, scattered, bilateral RH and retinal detachment was found in an infant with a mentally ill homeless mother and severe signs of malnourishment, and abuse could not be ruled out (Hendrickson et al., 2010). In such a case, it may have been AHT that was the cause of the RH rather than the coagulopathy.

We do recommend laboratory studies for coagulopathy when the cause of RH is not obvious and there is clinical suspicion of AHT. Recommendations for the evaluation of bleeding disorders in children with ICH suspicious for AHT have been published (Anderst, Carpenter, Abshire, Section on, H. O., Committee on Child, A., & Neglect of the American Academy of, & P., 2013; Carpenter, Abshire, Anderst, Section on, H. O., Committee on Child, A., & Neglect of the American Academy of, & P., 2013). These recommendations were based on the prevalence of specific congenital bleeding disorders and the prevalence of ICH within each specific congenital bleeding disorder. The recommended initial testing strategy includes complete blood count, PT, PTT, and specific activity levels of Factor VIII and Factor IX. Further testing may be warranted in some circumstances. It is important to note that this recommended testing strategy was based solely on bleeding disorder and ICH prevalence and not on known RH findings in specific bleeding disorders. Therefore, in clinical scenarios where a suspected victim of AHT has ICH and RH highly consistent with AHT, such as retinoschisis or folds, the testing strategy may be modified. Furthermore, given the lack of supporting data to suggest that bleeding disorders are the cause of retinoschisis or folds, suggestions that bleeding disorders caused such findings are not scientifically valid. TBI alone can cause changes in PT, aPTT, INR, and platelet count, indicating TIC. However, most cases of TBI with TIC present with mild to moderate coagulopathy, making it an unlikely direct cause of RH, especially severe, and certainly not a cause of retinoschisis or retinal folds. In outlier cases, evidence of severe recognizable accidental trauma is usually present.

We have reviewed all reported cases, to our knowledge, of pediatric coagulopathy associated with RH. A summary of those cases within the usual AHT age range (<5 years old) with RH are presented in Tables 1–4. In Table 1, cases are listed where abuse is eliminated outright based on systemic or retinal findings that suggest a medical etiology, such as cotton wool spots or exudative retinal detachment. Table 2 summarizes those cases in which the RH were non specific as to etiology or occurring at an age when they are indistinguishable from birth RH. Table 3 summarizes cases in which there was insufficient information provided about the RH to rule out/in abuse. The remaining 5 cases in which retinal findings could potentially be confused for abuse are summarized in Table 4. Several of these report VH, which is a notably rare finding in AHT, occurring in approximately 11 % of cases (Bhardwaj et al., 2010). None of these five cases presented with clinical history or systemic findings suggestive of abuse (i.e. SDH, fracture). AHT is ultimately diagnosed with a multidisciplinary team that considers multiple factors when deciding whether or not RH are consistent with abuse or other causes. Our review suggests, within the limits of such a review, that coagulopathy alone rarely should be considered as the etiology RH more suggestive of AHT, and only then in the absence of other indicators of abuse with specific coagulopathies as detailed herein.

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## Declaration of Competing Interest

The authors report no declarations of interest.

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