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A two-center retrospective review of the hematologic evaluation and laboratory abnormalities in suspected victims of non-accidental injury[☆]

Allison Paroskie^{a,*}, Shannon L. Carpenter^b, Deborah E. Lowen^c, James Anderst^b, Michael R. DeBaun^c, and Robert F. Sidonio Jr.^c

^aVanderbilt University, Nashville, TN, USA

^bChildren's Mercy Hospitals and Clinics, Kansas City, MO, USA

^cMonroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN, USA

Abstract

Investigation for bleeding disorders in the context of suspected non-accidental injury (NAI) is inconsistent. We reviewed the hematologic evaluation of children who presented with symptoms of bleeding and/or bruising suspicious for NAI to determine the frequency of hematologic tests, abnormal hematologic laboratory results, and hematologic diagnoses. A retrospective cohort study design was employed at two freestanding academic children's hospitals. ICD-9 codes for NAI were used to identify 427 evaluable patients. Medical records were queried for the details of clinical and laboratory evaluations at the initial presentation concerning for NAI. The median age for the population was 326 days (range 1 day–14 years), 58% were male. Primary bleeding symptoms included intracranial hemorrhage (31.8%) and bruising (68.2%). Hematologic laboratory tests performed included complete blood cell count in 62.3%, prothrombin time (PT) in 55.0%, and activated partial thromboplastin time (aPTT) in 53.6%; fibrinogen in 27.6%; factor activity in 17.1%; von Willebrand disease evaluation in 14.5%; and platelet function analyzer in 11.7%. Prolonged laboratory values were seen in 22.5% of PT and 17.4% of aPTT assays; 66.0% of abnormal PTs and 87.5% of abnormal aPTTs were repeated. In our cohort, 0.7% (3 of 427) of

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*Corresponding author address: Department of Pathology, Microbiology and Immunology, Vanderbilt University, 4800XA TVC, 1301 Medical Center Drive, Nashville, TN 37232, USA.

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Contributor's statement

Allison Paroskie, MD MSCI: Dr. Paroskie conceptualized and designed the study, performed data collection, carried out the initial analyses, drafted the initial manuscript, and approved the final manuscript submitted. Shannon L. Carpenter, MD contributed to the design of the study, performed data collection, reviewed and revised the manuscript and approved the final manuscript as submitted. Deborah E. Lowen, MD, James Anderst, MD MSci, Michael R. DeBaun, MD MPH, and Robert F. Sidonio Jr, MD MSC all contributed to the design of the study, reviewed and revised the manuscript and approved the final manuscript as submitted.

the population was diagnosed with a condition predisposing to bleeding. In children with bleeding symptoms concerning for NAI, hemostatic evaluation is inconsistent. Abnormal tests are not routinely repeated, and investigation for the most common bleeding disorder, von Willebrand disease, is rare. Further research into the extent and appropriate timing of the evaluation is warranted.

Keywords

Abuse; Blood; Hematology; Bleeding disorders

Introduction

Child maltreatment is a frequent and devastating phenomenon throughout the United States. In 2011, there were over 3 million instances of suspected child maltreatment, approximately 20% of which were the result physical abuse or non-accidental injury (NAI; U.S. Department of Health and Human Services, 2011). Bruising is the most common presenting symptom in physical abuse (Johnson & Showers, 1985), and abusive head trauma, including intracranial hemorrhage (ICH), is the most common cause of death resulting from physical abuse (Duhaime et al., 1992; Kellogg, 2007). Bleeding disorders are estimated to exist in as much as 1% of the general population; for von Willebrand disease, the most common minor bleeding disorder, the estimations of prevalence within the general population range from 0.6 to 1.3% (Nichols et al., 2008). When bleeding disorders are identified in children who present with bruising or bleeding, the perceived likelihood of abuse could be altered dramatically. Incorrectly diagnosing NAI is potentially life altering for the child and family (Kocher & Dichtel, 2011). Despite the high incidence of NAI and the relative high aggregate prevalence of bleeding disorders, few studies have evaluated the frequency of bleeding disorders in children who have bleeding/bruising concerning for NAI.

Medical understanding of children suspected of child maltreatment has evolved since Kempe identified Battered-Child Syndrome in his 1962 manuscript (Kempe, Silverman, Steele, Droegemueller, & Silver, 1962). Victims of NAI have been identified as having both true bleeding diatheses and unexplained coagulation laboratory abnormalities (O'Hare & Eden, 1984). In a population of non-accidental head trauma patients, prolonged PT, decreased fibrinogen, and decreased platelet counts were associated with parenchymal brain damage (Hymel, Abshire, Luckey, & Jenny, 1997). Despite these associations, neither the frequency of coagulation laboratory abnormalities in the setting of NAI nor the pathophysiology of these changes have been extensively studied. The optimal hematologic evaluation of NAI is not well defined despite expert opinion-based publications (Liesner, Hann, & Khair, 2004; Minford & Richards, 2010; Thomas, 2004). More recently, the American Academy of Pediatrics (AAP) published guideline recommendations for the hematologic evaluation of children with suspected NAI. These recommendations are expert opinions based on clinical presentation and prevalence of bleeding disorders in the general population, and thus could benefit from research directly focused on the NAI population (Anderst, Carpenter, & Abshire, 2013). Increased evidence is needed to further clarify the optimal evaluation for bleeding disorders in suspected NAI. Additionally, the

pathophysiology of acquired hematologic abnormalities in NAI is unknown, particularly in cases involving head trauma.

To further investigate the hematologic findings in children suspected of experiencing NAI, we conducted a two-center retrospective cohort study. Our objectives for this study were: (a) to determine the frequency and extent of a hematologic evaluation performed in children with intracranial hemorrhage and/or bruising and concern for NAI, (b) to determine the frequency of abnormal coagulation laboratory studies at the time of acute injury and the frequency of follow-up of those abnormal tests, and (c) to determine the frequency of hematologic diagnoses within this population.

Methods

A retrospective observational study design was utilized. Potential participants for the study were identified by query of hospital billing data at two tertiary care children's hospitals from January 2007 through March 2012 and November 2009 through December 2011, respectively, for ICD-9 codes for child physical abuse (995.5, 995.50, 995.54, 995.55, 995.59). Inclusion criteria consisted of the following: age less than 18 years at presentation, clinical presentation concerning for NAI defined as referral for evaluation of child abuse, and clinical presentation including bleeding or bruising. Children with a known history of bleeding disorder prior to initial presentation were excluded. Institutional Review Board approval was obtained for this study at Vanderbilt University in Nashville, TN, and Children's Mercy Hospitals and Clinics in Kansas City, MO.

Data were collected by medical record review and relevant information was entered into REDCap™, a secure, web-based application for building and managing online surveys and databases (Vanderbilt University, 2012). Extracted data included both clinical history and laboratory evaluation from the initial hospital encounter (emergency department visit, plus admission when applicable); follow-up outpatient clinical or laboratory testing was not included. Clinical data consisted of details of the patient's initial presentation, including physical examination and imaging studies, hematology assessment, admission to general pediatric ward or intensive care unit, and discharge disposition. Bleeding symptoms (e.g., bruising or ICH) were noted based on reported physical exam findings and imaging studies. For analysis purposes, bruises, as documented in the physical examination section of the history and physical reports within the medical record, were categorized by the study team as concerning for NAI versus non-concerning for NAI (Table 1; Anderst et al., 2013; Jackson, Carpenter, & Anderst, 2012). Laboratory data recorded included complete blood count (i.e., differential and smear review, kidney and liver function tests, PT, aPTT, fibrinogen, coagulation factor activity levels, von Willebrand antigen, ristocetin cofactor activity and multimer analysis, platelet function analyzer (PFA-100®), and evaluation for defects in fibrinolysis [e.g., plasminogen activator inhibitor 1 activity, alpha-2-antiplasmin activity]). Data were collected at initial presentation and associated hospital admission. Patient mortality and/or disposition were also assessed. *A priori*, we defined both a basic and comprehensive hematologic evaluation for both bruising and ICH based on testing for the most common bleeding disorders. We defined a basic hematologic evaluation as a CBC, PT, and aPTT. We defined a comprehensive hematologic evaluation as CBC, PT, aPTT, factor

VIII, factor IX, and von Willebrand disease panel. Laboratory values were defined as abnormal if they were outside the normal reference ranges for the hospital laboratory; hematology and chemistry laboratory values were age-based reference ranges, and coagulation laboratory values were based on adult reference ranges.

Data were analyzed using SPSS version 20. Descriptive analyses included demographic information and the frequency of individual laboratory tests, hematologic diagnoses, and intensive care admission. Descriptive analyses for continuous variables included mean, median, maximum and minimum values, and standard deviation when the data were normally distributed. Categorical variables are presented as percentages, and continuous variables are presented as median and ranges. For analysis purposes, we compared children with ICH, with or without bruising, to those with bruising alone, and then we compared children with and without associated non-hematologic injury (e.g., fractures, burns). Comparison between subjects with ICH and those with bruising as the primary finding was performed for the frequency of laboratory testing using chi-square or Fisher's exact tests. Comparison of laboratory values between groups was performed using Mann-Whitney *U* test, as the data were not normally distributed. Logistic regression was used to determine influence of confounding factors and predicted probability of laboratory testing. The dependent variable was the presence or absence of a complete basic or comprehensive hematologic evaluation. The independent variables included presenting symptoms (primary ICH vs. bruising or presence or absence of non-hematologic injuries) and PICU admission (yes/no). Comparison of initial and repeated PT and aPTT values was performed using Wilcoxon Signed Ranks Test.

Results

Demographics and Presenting Findings

Over a five-year period, a total of 775 medical records were identified at the two institutions (hospital 1 and hospital 2); 348 individuals were eliminated based on our inclusion and exclusion criteria. The majority of children were eliminated because of a lack of bleeding or bruising (e.g., sibling examination). We analyzed a total of 198 participants at hospital 1 and 229 participants at hospital 2. The median age was 326 days (range 1 day–14 years), 58.3% of the population was male, and 65.1% of the population was Caucasian. (Complete demographic information can be found in Table 2.) The most common presenting bleeding symptom was isolated bruising, followed by bruising with other features such as fractures or burns (Table 2). All children in the study were referred for NAI evaluation, however, upon review of the physical exam findings, 75.6% of children presented with bruising that was documented in a manner that supported this referral (e.g., patterned bruising); approximately half of the children who presented with bruising concerning for NAI also demonstrated additional bruising that was not concerning for NAI.

Frequency of Hematologic Evaluation of NAI

Hemostatic laboratory testing was done in a subset of the population and was not uniformly performed. Within our cohort, 33.0% of participants did not have any laboratory evaluation. In those who had laboratory testing, the most common testing included CBC, PT, and aPTT.

When factor activity levels were obtained (17.1%), they consisted of mainly factors VIII (15.2%) and IX (16.6%); additional factors were rarely obtained (XII 0.9%, XI 2.3%, X 0.2%, VII 0.5%, V 0.5% and II 0.5%). Von Willebrand disease, with testing including both antigen level and ristocetin cofactor assay, occurred rarely (14.5%), as did assessment for qualitative platelet disorders via PFA-100® (11.7%).

Comparison of Hematologic Evaluations in ICH vs. Bruising Cases

Laboratory testing occurred more often in children with ICH (Fig. 1). The basic hematologic evaluation was completed in 80.9% of patients with ICH and 39.2% of patients with bruising ($p < 0.001$). The completion of the a priori defined basic hematologic evaluation occurred more frequently in patients with ICH versus patients with bruising, independent of admission to the intensive care unit (*OR*: 3.1, 95% CI [1.8, 5.4], $p < 0.001$). The comprehensive evaluation was completed in 16.2% of patients with ICH and 8.6% of patients with bruising ($p = 0.030$). No difference was detected between patients with ICH versus patients with bruising independent of admission to the intensive care unit ($p = 0.88$).

Comparison of Hematologic Testing in Subjects with Associated Injuries versus those Without Associated Injuries

The presence or absence of non-hematologic injuries (e.g., burns, fractures) had minimal impact on the frequency of basic hematologic testing. Our defined basic evaluation was completed in 60.2% of patients with associated injuries and 46.5% of those without associated injuries ($p = 0.006$), however in a logistic regression model including admission to the intensive care unit, this significance was no longer present ($p = 0.212$). Our defined comprehensive evaluation was completed in 7.0% of those with associated injuries and 14.1% of those without associated injuries ($p = 0.020$). After adjusting for admission to the intensive care unit, however, this significance was no longer present ($p = 0.088$).

High Prevalence of Prolonged Coagulation Laboratory Values with Low Frequency of Follow Up Evaluation

The presence of abnormal coagulation screening tests (PT and aPTT) did not consistently result in repeat testing. Prolonged coagulation laboratory values for PT and aPTT were seen in 22.5% (53 of 235 performed tests) and 17.4% (40 of 229 performed tests), respectively. The range of abnormal values for PT was 15 to 100 seconds ($M = 19.49$ s) and the range of abnormal values for aPTT was 20 to 185 seconds ($M = 42.17$ s). Prolonged PT values were more frequent in patients with ICH compared to bruising (29.4% vs. 15.5%, $p = 0.008$), and initial PT values were statistically significantly higher in ICH ($M = 23.01$ s) than bruising ($M = 18.15$ s, $p < 0.001$). The frequency of prolonged aPTT in each group (19.5% in ICH, 15.5% in bruising) was not statistically significant ($p = 0.270$).

Only 66.0% (35 of 53) of initially abnormal PT values received a repeat evaluation. The median time to a follow-up was 2.0 days (range 0–11 days), and the difference between mean values, 21.49 s at initial presentation and 15.79 s at repeat, was statistically significant ($p < 0.001$). In contrast, 87.5% of initially abnormal aPTT values received a repeat evaluation. The median time to a follow-up was 1.0 day (range 0–11 days), and the

difference between mean values, 45.1 s at initial presentation and 38.1 s at repeat, was not statistically significant ($p = 0.326$).

Conditions Predisposing to Bleeding in Our Cohort of Children Suspected of NAI

Within our cohort, 3 of 427 (0.7%) were diagnosed with a hematologic disorder or other predisposing medical condition that could aid in the explanation of their bleeding symptoms, and 0.7% (3 of 427) were undergoing evaluation when lost to follow-up. Of the three diagnosed children, two were diagnosed with bleeding disorders (late vitamin K deficiency and hemophilia A), and one was diagnosed with Osteogenesis Imperfecta, which although is not universally considered a bleeding disorder, the patient's bruising was attributed to this diagnosis (Table 3).

Discussion

To our knowledge, this is the first retrospective study investigating the scope of hematologic evaluation in children with suspected NAI. We have demonstrated that at two large referral centers, hematologic evaluation for children with NAI is inconsistently performed. A difference was noted between laboratory evaluations of children with ICH and bruising; however, the majority of these differences disappeared when admission to the intensive care unit (ICU) was considered in the analysis. ICU admission was only a confounding variable in more extensive hematologic evaluation. In addition, when abnormal hematologic laboratory results were identified, they were often not repeated.

Despite the varying hematologic evaluation in this cohort, two children with suspected NAI were identified as having a disease associated with excessive bleeding (late vitamin K deficiency bleeding and severe hemophilia A), which were identified due to prolonged PT (>100.0 s) and aPTT (116.9 s), respectively. Both of these diagnoses were made within 24 h of initial presentation because of the clinical team obtaining early screening laboratory data. In addition, one child was diagnosed with a disease (Osteogenesis Imperfecta) that could potentially predispose an individual to bleeding symptoms (Evensen, Myhre, & Stormorken, 1984; Hathaway, Solomons, & Ott, 1972). This diagnosis was made based on laboratory evaluation obtained due to increased clinical concern for easy fractures. These three children were ultimately not considered victims of NAI by the managing clinicians. Given the inconsistencies in the hematologic evaluations, additional hematologic diagnoses may have been present and unidentified. The most common bleeding disorder, von Willebrand disease, was rarely tested for in this study. As such, the frequency of children with NAI and low von Willebrand levels within our cohort is unknown. Further study regarding von Willebrand disease and low von Willebrand factor in this population is warranted.

The most unexpected finding in our cohort was the high frequency of prolonged PT and aPTT. Children who underwent a hemostatic evaluation had a prolonged PT or aPTT approximately 20% of the time; the percentage of abnormally prolonged PT tests was even higher in the ICH population. The etiology of these laboratory abnormalities is unclear. A portion of these abnormalities could be secondary to dilution from drawing from an indwelling catheter, however it is unlikely that initial labs, obtained at the time of presentation, would be subject to this false-positive prolongation. In addition, it is unclear

from our data collection, which did not include follow-up laboratory testing beyond the initial admission, if these prolongations were permanent or transient. Only 4% of our cohort was seen by the hematology team, thus follow-up testing to clarify the etiology of these abnormalities is unlikely to have occurred. It has been postulated that PT prolongation after traumatic brain injury is secondary to tissue factor release from damaged parenchymal tissue (Hymel et al., 1997), however, this explanation does not explain our high rate of prolonged aPTT or the presence of abnormal PT or aPTT in patients with bruising and no head injury. Hematology follow-up would allow identification of transient abnormalities that could result in falsely normal testing (e.g., von Willebrand factor is an acute phase reactant, thus could be elevated to normal levels despite disease) or falsely abnormal testing (e.g., consumption of coagulation factors secondary to injury resulting in decreased activity).

The laboratory abnormalities noted in this population are further complicated by a lack of consistent repeat laboratory testing to clarify if the abnormalities are transient (e.g., disseminated intravascular coagulation, transient antiphospholipid antibody) or represent the presence of a true bleeding diathesis. Given the rate of bleeding disorders in the general population, a reasonable assumption is that a significant portion of these abnormalities are secondary to transient or acquired abnormalities related to the clinical presentation. We postulate that the transient abnormal laboratory results reflect a combination of multiple mechanisms, including activation of the coagulation system or decreased fibrinogen and hyperfibrinolysis. These proposed mechanisms are similar to the postulated mechanisms that occur in accidental trauma; wherein approximately 25% of major trauma victims have prolonged PT and aPTT (Sidonio, Gunawardena, Shaw, & Ragni, 2012).

This retrospective cohort study has a number of limitations. First, as with any retrospective database, there is the concern of overestimation of abnormalities within the cohort. Second, the rationale for clinical decisions, such as obtaining laboratory data, was not explained in the medical record. In addition, the rationale for concern of NAI was not captured in our data, thus potentially limiting our understanding of the management decisions.

Approximately 30% of the patients in our cohort did not have any laboratory evaluation and we are unable to identify the reasoning behind this. Some of the patients may have demonstrated pathognomonic signs and symptoms of child abuse thus the providers did not feel a hematologic evaluation was warranted; however collection of this data was outside the scope of this study. The evaluation of suspected child abuse is a multi-disciplinary collaborative process, involving investigative and medical components. It is possible that the results of this collaborative process at our institutions affected the extent of the hematologic evaluation. In addition, while comprehension of rationale is ideal, our study was designed to evaluate the extent of the hematologic evaluation performed on these children regardless of rationale. The data collection methodology most likely missed a portion of subjects (Hooft, Ronda, Schaeffer, Asnes, & Leventhal, 2013). Participants were identified via ICD-9 codes for child maltreatment, thus any children who were not provided with a 995 ICD-9 code would have been excluded from the study. This technique relies on physician coding and thus may miss any child who did not have a final diagnosis of abuse (e.g., a child who was diagnosed with a bleeding disorder resulting in altered concern for abuse). Both academic referral centers in this study currently have board certified child abuse pediatricians who perform medical evaluation of cases of suspected child abuse. One site did not have a child

abuse pediatrician until August 2010, thus children in the cohort seen prior to that time were evaluated by general pediatricians who may have had different evaluation and coding practices. In addition, children who present with concern for NAI to a facility without a child abuse pediatrician may have a different evaluation. This discrepancy of approach highlights the importance of developing a standard of care for these children. Our cohort included a large number of subjects, suggesting that the missed cases (e.g. due to use of ICD-9 codes) would not have greatly affected the results or conclusions.

Conclusion

Our data suggest that hematologic evaluation of children with bleeding and/or bruising in the context of suspicion of NAI is not uniform. In addition, among children suspected for NAI, prolonged PT and aPTT are common at presentation and seen regardless of the type of bleeding symptoms present. Both of these observations support the need for further study in this population. The variability in the hematologic evaluation of these children could result in missed or misunderstood diagnoses and thus emphasizes the necessity of standardized evaluation of this patient population as recently recommended by the AAP (Anderst et al., 2013). We believe there is currently an information gap between the AAP recommendations and the optimal hematologic strategy for evaluation of NAI due to the lack of research focused directly on this patient population. This study is the first step to identify information gaps. Going forward, a prospective study with standardized hematologic testing may be required to further clarify the frequency and nature of bleeding diatheses and the physiologic basis for such abnormalities in this population. In addition, comparison of children who demonstrate bleeding due to NAI versus accidental trauma would provide insight into the pathophysiology of prolongation of PT and aPTT tests. Such data could improve the understanding of the physiology of bleeding symptoms in the population and improve the evidence basis for decision-making in the hemostatic evaluation of children with suspected NAI.

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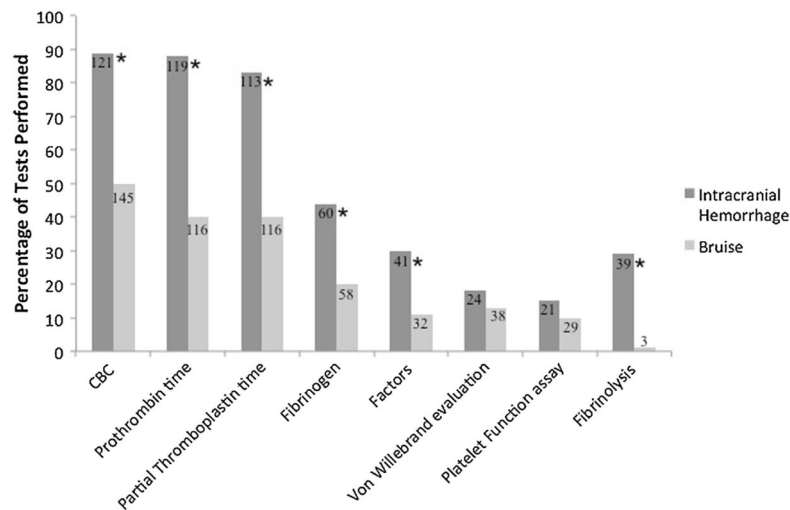


Fig. 1. Percentage of subjects with individual laboratory tests performed at any time during their evaluation divided by presenting hematologic symptoms: intracranial hemorrhage with or without bruising ($n = 137$) or bruising alone ($n = 290$). The absolute number of children who received testing is within each bar. * p value < 0.001 for comparison of testing frequency between ICH and bruising.

Table 1

Characteristics of bruises that are more and less suspicious for non-accidental injury (NAI).

Bruising less suspicious for NAI	Bruising more suspicious for NAI
Location	Location
Forehead	Face (excluding forehead)
Head (excluding forehead, face or ear)	Neck
Distal arms (including elbow)	Abdomen
Spinous/paraspinous	Proximal arms (above elbows)
Anterior and posterior legs (e.g. shins, knees, calves)	Ear
Oral	Buttocks
Hips	Genital
Ankle	Anterior or posterior thigh
	Back (excluding spinous/paraspinous)
	Anterior or lateral chest
	Foot
	Hand
	Wrist
	Characteristics
	Symmetric
	Paternal
	Any bruising in a child < 9 months old

Table 2

Demographics and presenting symptoms for all children, divided by hospital and total. “Additional symptoms” is defined as any non-hematologic injury noted on physical exam or imaging (e.g. fractures, burns).

	Hospital 1 (n = 198)	Hospital 2 (n = 229)	Total (n = 427)
Age, median (range)	273 days (6 days–13 years)	354 days (1 day–14 years)	326 days (1 day–14 years)
Gender			
Male	63.1%	54.1%	58.3%
Female	36.9%	45.9%	41.7%
Ethnicity			
Hispanic or Latino	6.1%	9.6%	8.0%
Not Hispanic or Latino	30.8%	15.7%	22.7%
Unknown	63.1%	74.7%	69.3%
Race			
Black or African American	22.2%	10.9%	16.2%
Asian	2.0%	1.3%	1.6%
White/Caucasian	58.1%	71.2%	65.1%
Other or unknown	6.1%	13.1%	9.8%
Multi-Racial	11.6%	3.5%	7.3%
ICH with or without bruising	15.7%	12.7%	14.1%
ICH with or without bruising and additional symptoms	24.7%	11.8%	17.8%
Bruising	29.3%	53.7%	42.4%
Bruising and additional symptoms	30.3%	21.8%	25.7%

Table 3

Clinical descriptions and evaluations of the three patients who were diagnosed with disorders that would predispose to bleeding symptoms.

Diagnosis	Clinical presentation	Evaluation	Additional comments
Late Vitamin K deficiency	Previously well 3-month-old male who presented with jaundice, new seizure activity and intracranial hemorrhage.	Initial: PT > 100 s, aPTT 184.5 s Follow-up: PT & aPTT improved with plasma transfusion. No factor activities obtained.	The baby was ultimately diagnosed with cholestatic liver disease, which resulted in vitamin K, A and D deficiency, as well as failure to thrive.
Hemophilia A	Previously well 5-month-old male who presented with enlarging hip bruise and prior history of cephalohematoma.	Initial: PT 13.3 s, aPTT 116.9 s Follow-up: factor VIII <1%, factor IX 66%, factor XII 39%	Repeat testing demonstrated persistence of factor VIII activity reduction. Hematology consult obtained due to isolated laboratory abnormality.
Osteogenesis Imperfecta	6 month old with previously diagnosed Osteogenesis Imperfecta (COL1A1 mutation) presented with bilateral frontal subdural hemorrhages, acute and subacute, without skull fracture after a witnessed fall.	Ophthalmology evaluation for retinal hemorrhages: negative. Skeletal survey: negative. Hematologic laboratory evaluation: normal.	