Coagulopathy in Pediatric Abusive Head Trauma

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ABSTRACT. *Objectives.* **Coagulopathy is a potential complication of head trauma that may be attributable to parenchymal brain damage. The objectives of this study were to assess the frequency of coagulation defects in pediatric *abusive* head trauma and to analyze their relationship to parenchymal brain damage.**

Methods. **We reviewed the records of 265 pediatric patients hospitalized for head trauma. One hundred forty-seven patients met study inclusion criteria: (1) radiologic evidence of head trauma, (2) multidisciplinary validation that head trauma had been inflicted, and (3) coagulation screening performed within 2 days of presentation. Using nonparametric analysis, initial coagulation test results were compared between study patients *without* parenchymal brain damage and those *with* parenchymal brain damage.**

Results. **Mild prothrombin time (PT) prolongations (median 13.1) occurred in 54% of study patients *with* parenchymal brain damage and only 20% of study patients *without* parenchymal brain damage. Among pediatric abusive head trauma patients with parenchymal brain damage *who died*, 94% displayed PT prolongations (median 16.3) and 63% manifested evidence of activated coagulation.**

Conclusions. **PT prolongation and activated coagulation are common complications of pediatric abusive head trauma. In the presence of parenchymal brain damage, it is highly unlikely that these coagulation abnormalities reflect a preexisting hemorrhagic diathesis. These conclusions have diagnostic, prognostic, and legal significance.** ***Pediatrics*** **1997;99:371–375;** ***child abuse, head trauma, coagulopathy.***

ABBREVIATIONS. DIC, disseminated intravascular coagulation; PT, prothrombin time; CT, computed tomography; MRI, magnetic resonance imaging; PTT, activated partial thromboplastin time; TT, thrombin time; FDP, fibrin degradation products.

Only a single prospective study has reported coagulopathy to be a potential complication of pediatric head trauma.[1] Case records of these 87 consecutive children indicated that minor hemostatic abnormalities were very common after traumatic head injury. Mortality was correlated with destruction of brain tissue and the presence of disseminated intravascular coagulation (DIC).

In adults, a coagulopathy that correlates with poor survival has been recognized as a complication of traumatic brain injury.[2–7] Delayed brain injury may be the consequence of an acquired coagulopathy in such cases.[8] If coagulation abnormalities are discovered at presentation, the risk of delayed brain injury in adults after head trauma increases significantly.[9,10]

A plausible hypothesis is that tissue factor released from damaged brain parenchymal cells binds to factor VII, causing activated coagulation and prolongation of the prothrombin time (PT). The tissue factor-factor VII complex activates factor X and prothrombin, occasionally leading to DIC with consequent hemorrhage. Further prospective studies will be required to verify this hypothesis.

We reasoned that coagulation abnormalities should also occur in pediatric *abusive* head trauma. Although this conclusion seems obvious, it has significant legal implications for practitioners who must testify in cases of pediatric inflicted head trauma. When coagulopathy is identified, appropriate child protection efforts may be terminated because of premature assertions that these coagulation abnormalities represent a preexisting hemorrhagic diathesis. Clear evidence that coagulopathy is a frequent complication of abusive head trauma is essential.

The main objectives of this study were to assess the frequency of coagulation defects in pediatric inflicted head trauma and to analyze their relationship to parenchymal brain damage. Our conclusions have diagnostic, prognostic, and legal significance.

METHODS

Patient Selection

The medical records of 265 pediatric patients with head trauma evaluated specifically for child abuse at the Children's Hospital in Denver, Colorado, between 1982 and 1995 were retrospectively reviewed. Records selected for inclusion in this study met the following criteria: (1) unequivocal computed tomography (CT) and/or magnetic resonance imaging (MRI) scan evidence of head trauma, (2) clear validation by a multidisciplinary child protection team that the head trauma had been inflicted, and (3) coagulation screening parameters performed within 2 days of presentation.

In this study, there was variability over the 13-year period in makeup of the multidisciplinary child protection team, expertise of radiographic reviewers, knowledge and application of emerging criteria for the diagnosis of child abuse, and cranial imaging technology, sensitivity, modality, and/or frequency. Accordingly, a conservative application of study inclusion criteria was deemed essential.

The principal reasons for record exclusion from the study were: lack of acute coagulation screening (N = 70), equivocal results of multidisciplinary case review (N = 21), statistical listwise deletion

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of records lacking complete coagulation screening (N = 16), and absent or equivocal neuroimaging results (N = 12). To partially exclude the effects of tissue factor release from noncranial sources, patients with severe, noncranial soft tissue injuries at presentation (N = 7) were also excluded. Eight records had two or more principle reasons for study exclusion. In light of a previous study that reported fractures were of minimal importance as a cause of coagulopathy in head trauma,[2] patients with fractures were not excluded.

Radiologic Findings

Cranial CT and/or MRI imaging results were used to separate patients into two radiologic categories based on the presence or absence of parenchymal brain damage. Parenchymal brain damage was said to be present if there was radiologic evidence of localized brain parenchymal bleeding/contusion, frontal/parietal shearing, basal ganglia edema, cerebral edema, diffuse axonal injury, hypoxic ischemic encephalopathy, and/or (later) cerebral atrophy.

Initial Coagulation Testing

Statistical analysis was based on initial coagulation tests only. In this study, an *initial* coagulation value was defined as the first coagulation test result if obtained within 2 days of presentation for inflicted head trauma. All repeat coagulation test results were excluded from the statistical analyses. Based on the inherent unreliability of the history in cases of abusive head trauma and possible delays in seeking medical care, the actual time period between injury and initial coagulation testing may have been longer than 2 days.

The coagulation test results initially considered in this study fall into the screening category: PT, activated partial thromboplastin time (PTT), thrombin time (TT), bleeding time, platelet count, fibrinogen, fibrin degradation products (FDP), and hematocrit. In this retrospective study, bleeding time and FDP testing were carried out infrequently and therefore were not analyzed.

Coagulation Testing Methodology

The initial coagulation testing of 145 of 147 study patients (99%) was performed at The Children's Hospital, Denver, Colorado, within 2 days of admission for acute inflicted head trauma. The methodology for coagulation testing at The Children's Hospital is summarized below.

For patients admitted before 1990, PT and PTT testing were accomplished manually using the MLA (Medical Laboratory Automation, Inc, Pleasantville, NY) optical instrument. For more recent patients, PT and PTT testing were performed using an ACL 300 (Automated Coagulation Laboratory, Lexington, MA) instrument and reagents provided from Instrumentation Laboratory. TT was completed manually on a fibrometer device with Thrombostat thrombin reagent provided by Parke-Davis, Inc (Morris Plains, NJ). Bleeding time was accomplished using a General Diagnostics Simplate (Durham, NC) puncturing device. Platelet count and hematocrit determinations were performed using an automated Coulter Max-M (Miami, FL) unit. Fibrinogen values were calculated from the PT curve obtained with the ACL 300 (Automated Coagulation Laboratory) unit and PT-Fibrogen (derived) reagent supplied by Instrumentation Laboratory (Lexington, MA). FDP testing was completed manually using a latex agglutination kit from Diagnostica-Stago (Asnieres-sur-Seine, France).

Analysis of Initial Coagulation Test Results

The principal focus of this study was to explore the relationship of coagulation abnormalities to parenchymal brain damage. For this primary analysis, the results of initial coagulation testing were compared between study patients *without* parenchymal brain damage and those *with* parenchymal brain damage. In a secondary analysis, we sought to identify those coagulation tests which differentiated between survival and death in abusive head trauma patients *with* parenchymal brain damage. Cases lacking one or more of the coagulation test results considered in each analysis were deleted before statistical comparison. The percentage of abnormal coagulation test results in each patient category were tabulated to facilitate group comparisons. Because coagulation values were found to be highly skewed in both the primary and secondary analyses, the data were reported as medians and percentiles and the nonparametric Wilcoxan rank sum test was used rather than a Student's t test.

Evidence of Activated Coagulation

Probable evidence of activated coagulation (and presumptive evidence of DIC) was defined as: a moderately elevated PT ($\geq$16 seconds) not attributable to vitamin K deficiency or liver disease, an elevated PT and PTT, or an elevated PT in conjunction with a low platelet count, low fibrinogen, and/or a positive FDP. The relationships of probable activated coagulation to parenchymal brain damage and to death were assessed using χ^2 analysis.

RESULTS

Patient Demographics

The final patient sample of 147 patients included 84 male and 63 female patients. The median age of the study sample of pediatric inflicted head trauma patients was 4.5 months, with an age range of 2 weeks to 3 years, 7.5 months.

Radiologic Cranial Imaging Results

Forty-six of 147 patients (31%) were classified as having no radiologic evidence of parenchymal brain damage as previously defined (median age 5 months). The remaining 101 patients (69%) demonstrated unequivocal CT and/or MRI scan evidence of parenchymal brain damage (median age 4 months). All 32 study patients who died (100%) displayed radiologic evidence of parenchymal brain injury, whereas only 69 of 115 survivors (60%) demonstrated such findings ($P < .0001$).

Patients Without Parenchymal Brain Damage vs Patients With Parenchymal Brain Damage

In Table 1, the results of initial PT, PTT, hematocrit, and platelet count testing are compared between study patients *without* parenchymal brain damage (N = 46) and those *with* parenchymal brain damage (N = 101). The number of thrombin time and fibrinogen results were too small (<10) for statistical inclusion in this primary analysis. Whereas 55 of 101 study patients with parenchymal brain damage (54%) manifested initial PT prolongations, only 9 of 46 study patients lacking parenchymal brain damage (20%) had prolongations of initial PT ($P = .0001$). Statistically highly significant differences ($P = .0001$) in initial PT values between these two groups were revealed. Although PT prolongations in study patients with parenchymal brain damage appeared to be clinically mild [median 13.1; range (5th-95th percentile) 11.2–18.1], results were highly skewed (see Fig 1). Severe PT prolongations were evident in several patients with parenchymal brain damage. Statistically significant differences in initial PTT, hematocrit, and platelet count were also noted.

Patients With Parenchymal Brain Damage/Survived vs Patients With Parenchymal Brain Damage/Died

In Table 2, the results of initial PT, PTT, hematocrit, platelet count, TT, and fibrinogen testing are compared between study patients with parenchymal brain damage who survived (N = 69) and those who died (N = 32). In this secondary comparison, statis-

TABLE 1. Initial* Coagulation Test Results: *Without* Parenchymal Brain Damage vs *With* Parenchymal Brain Damage

Coagulation Test	Normal Values (Mean ± 2 SD)	*Without* Parenchymal Brain Damage				*With* Parenchymal Brain Damage				Wilcoxon *P* Value
		(n)	Median	(5th–95th Percentile)	Abnl (%)†	(n)	Median	(5th–95th Percentile)	Abnl (%)†	
PTs	11.8 ± 1.0	46	12.0	10.9–13.7	20	101	13.1	11.2–18.1	54	.0001
PTTs		46	27.0	23.0–36.3	9	101	30.2	21.1–63.4	24	.0155
<6 months old	30.5 ± 5.3									
>6 months old	27.7 ± 5.2									
Platelets ($10^3/mm^3$)	315 ± 185	46	528	290–806	0	101	411	199–728	1	.0009
Hematocrit (%)	35.0 ± 7.0	46	32.4	24.6–40.7	15	101	27.5	19.1–37.1	45	.0001

Abbreviations: (n), number of specific test results analyzed after deletion of cases lacking one or more coagulation variables; PT, prothrombin time; PTT, activated partial thromboplastin time; SD, standard deviation.
* Initial = first coagulation test results if obtained within 2 days of clinical presentation; see text.
† Abnl (%) refers to percentage of test results analyzed that fell outside the established normal range for age. Initial coagulation abnormalities tabulated include: PT, PTT elevation (>2 SD) and platelet count, hematocrit depression (<2 SD).

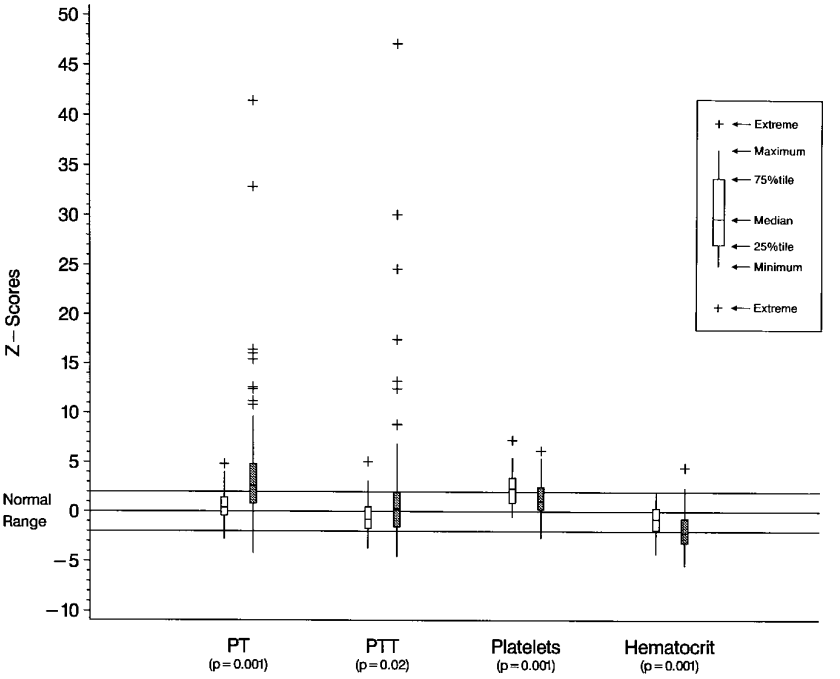

Fig 1. Comparison of initial coagulation values for pediatric inflicted head trauma patients *without* (unshaded) and *with* (shaded) parenchymal brain damage. *P* values were derived with the Wilcoxon rank sum test.

tically significant differences ($P = .0019$) in initial PT values between these two groups were again noted. Ninety-four percent of study patients with parenchymal brain damage *who died* demonstrated PT prolongations that were more clinically severe [median 16.3; range (5th-95th percentile) 12.4–32.5]. As in the primary analysis, results were highly skewed (see Fig 2). Statistically significant differences in initial platelet count and fibrinogen values were also noted.

Evidence of Activated Coagulation

Whereas 37 of 101 patients with parenchymal brain damage (37%) revealed probable evidence of activated coagulation as previously defined, only 3 of 46 study patients without parenchymal brain damage (7%) revealed these changes ($P = .0001$). Further analysis also revealed a strong correlation between probable evidence of activated coagulation and death. Whereas only 20 of 115 survivors of abusive head trauma (17%) revealed probable evidence of activated coagulation, 20 of 32 study patients who died (63%) displayed this pattern ($P < .0001$).

DISCUSSION

Exclusion of Preexisting Bleeding Diatheses in Study Patients

Although limited by our retrospective study design, an effort was made to screen study patient records for preexisting bleeding diatheses. Medical records of study patients did not reveal clinical suspicion of a bleeding disorder, vitamin K deficiency, home delivery, or liver disease. Documentation of vitamin K prophylaxis perinatally was frequently absent from inpatient records at the time of head trauma. However, vitamin K deficiency is uncommon. Estimates of the incidence of classic hemorrhagic disease of the newborn before prophylaxis began range from 1 in 200 to 400 births.[11] Although preexisting hemorrhagic diatheses were not definitively excluded in this retrospective study, the probability of clinically significant, preexisting hemor-

TABLE 2. Initial* Coagulation Test Results: Parenchymal Brain Damage/*Survived* vs Parenchymal Brain Damage/*Died*

Coagulation Test	Normal Values (Mean ± 2 SD)	Parenchymal Brain Damage/*Survived*				Parenchymal Brain Damage/*Died*				Wilcoxon *P* Value
		(n)	Median	(5th–95th Percentile)	Abnl (%)†	(n)	Median	(5th–95th Percentile)	Abnl (%)†	
PTs	11.8 ± 1.0	25	12.8	11.4–19.8	48	16	16.3	12.4–32.5	94	.0019
PTTs		25	31.0	23.0–76.6	28	16	33.7	24.2–91.5	44	.1344
<6 months old	30.5 ± 5.3									
>6 months old	27.7 ± 5.2									
Platelets (10^3/mm^3)	315 ± 185	25	414	258–814	0	16	302	68–544	6	.0085
Hematocrit (%)	35.0 ± 7.0	25	24.3	19.2–37.1	72	16	25.7	17.9–43.2	56	.3226
TTs	11.0 ± 2.5	25	13.0	8.5–33.0	44	16	12.5	5.8–19.0	44	.4137
Fibrinogen (mg/dL)	283 ± 110	25	285	101–423	20	16	174	88–348	50	.0099

Abbreviations: (n), number of specific test results analyzed after deletion of cases lacking one or more coagulation variables; PT, prothrombin time; PTT, activated partial thromboplastin time; TT, thrombin time; SD, standard deviation.
* Initial = first coagulation test results if obtained within 2 days of clinical presentation; see text.
† Abnl (%) refers to percentage of test results analyzed that fell outside the established normal range for age. Initial coagulation abnormalities tabulated include: PT, PTT, TT elevation (>2 SD) and platelet count, hematocrit, fibrinogen depression (<2 SD).

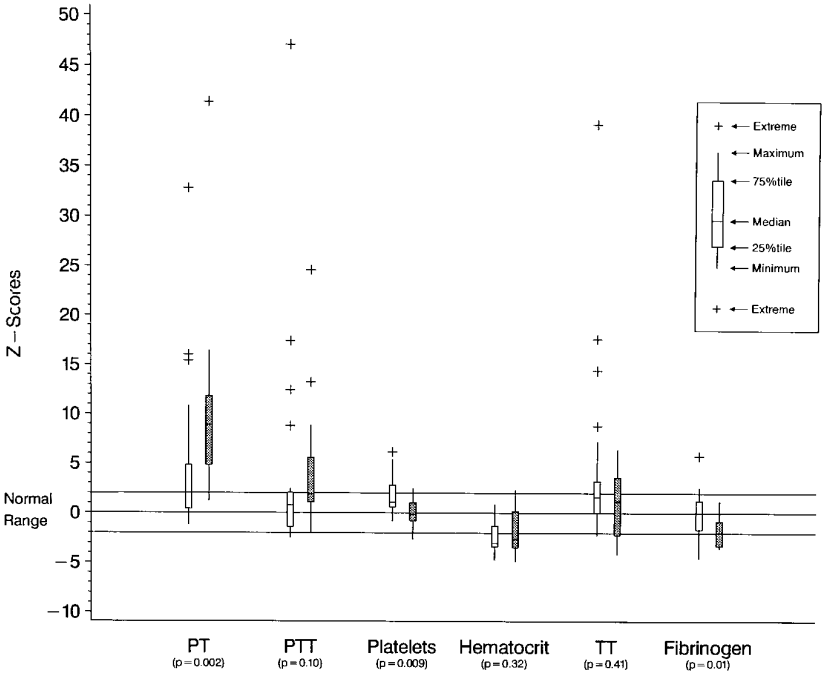

Fig 2. Comparison of initial coagulation values for pediatric inflicted head trauma patients with parenchymal brain damage who *survived* (unshaded) and *died* (shaded). *P* values were derived with the Wilcoxon rank sum test.

rhagic diathesis in study patients was estimated to be very low.

Pathophysiology

Several reports have correlated head trauma with DIC and subsequent bleeding in adults. Kaufman and colleagues[10] demonstrated delayed bleeding after traumatic head injury in 87% of their patients who presented with DIC. By correlating laboratory with histopathological evidence of DIC, these authors verified that more severe head trauma produced greater coagulation abnormalities and pathological evidence of microthrombi. Kearney et al[6] demonstrated mortality after head injury to be related to decreased platelet count, decreased fibrinogen, and elevated PT—values all consistent with DIC. Finally, Stein and colleagues[9] reported that the risk of delayed brain injury and bleeding after head trauma increased to 85% if coagulation testing was abnormal on admission. These delayed complications of adult head trauma were significantly correlated with PT prolongation. The time interval between brain injury and secondary coagulopathy has been variously estimated from hours to days.[7,8]

Evidence exists for thrombin activation rather than primary fibrinolysis as the basis for the coagulopathy found in adult head trauma patients. Goodnight et al[8] were the first to suggest this relationship in traumatic brain injury. Subsequently, investigators used more specific markers of thrombin activation (fibrinopeptide Bβ 15–42, D-dimer, thrombin/antithrombin complex and prothrombin fragment F 1+2) to investigate the pathophysiology and severity of the coagulopathy of adult head trauma.[4,12,13] These markers were significantly higher in patients with more severe head trauma and when the coagulopathy was secondary to DIC. In two of these reports, therapeutic intervention with anticoagulants was initiated and levels of these thrombin activation peptides were followed to ascertain treatment effectiveness.[4,12]

Only a single study to date describes the frequency and implications of DIC in children after traumatic head injury.[1] DIC was present in one third of their patient population and mortality increased fourfold

when DIC was present. More severe head trauma produced a greater degree of coagulopathy and DIC. Remarkably, the frequency of at least one abnormal screening coagulation test occurring after head trauma was 71%. In this study, even trivial head trauma (by history) could produce coagulation changes.

Coagulopathy is a potential complication of severe head trauma, including pediatric abusive head trauma. Though not specific for child abuse, PT prolongation and/or activated coagulation occurred frequently in our study sample of pediatric patients with inflicted parenchymal brain damage. An isolated, elevated PT is often the result of depressed factor VII. In the absence of vitamin K deficiency, liver disease, or inherited factor VII deficiency, PT prolongation can only be the result of tissue factor release and subsequent consumptive coagulopathy. We hypothesize that head trauma causes tissue factor release from damaged brain parenchymal cells. Tissue factor/factor VII complex can subsequently activate coagulation via the extrinsic pathway, in some cases leading to DIC. A prospective study of coagulation profiles in pediatric head trauma, including assays for activated factor VII,[14] tissue factor production, and markers of thrombin activation, should be carried out to confirm this hypothesis.

RECOMMENDATIONS

For prognostic reasons, we would recommend that patients with suspected traumatic parenchymal brain injury have the following coagulation screening tests performed on presentation: PT, PTT, TT, complete blood count, platelet count, fibrinogen, and FDP or D-Dimer. Serial monitoring for DIC may be required. Discovery of a prolonged PT or evidence of activated coagulation should prompt a thorough patient/family history for bleeding diathesis. In cases of suspected pediatric *abusive* head trauma, discovery of PT prolongation or DIC should not interfere with appropriate legal child protection efforts.

Liver disease or vitamin K deficiency should be considered. Infants less than 6 months old who had perinatal complications, are receiving antibiotics, or are breastfed are at greatest risk for vitamin K deficiency. Correction of a coagulopathy after vitamin K administration provides confirmation of this deficiency.[11]

CONCLUSIONS

Coagulopathy is a frequent complication of head trauma, including pediatric abusive head trauma. In our study, PT prolongation and activated coagulation were strongly related to the presence of parenchymal brain damage. Among study patients who died, these coagulation abnormalities were more frequent and severe. In the presence of parenchymal brain damage, it is highly unlikely that these coagulation abnormalities are attributable to a preexisting hemorrhagic diathesis. These conclusions have diagnostic, prognostic, and legal significance.

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