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Hemorrhagic Stroke in Term and Late Preterm Neonates

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Abstract

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All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have approved the final version for submission.
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Objective—Few data regarding causes and outcome of hemorrhagic stroke (HS) in term neonates are available. We characterized risk factors, mechanism, and short-term outcomes in term and late preterm neonates with acute HS.

Design—Prospective cohort.

Setting—Single-center tertiary care stroke registry.

Subjects—Term and late preterm neonates (≥34 weeks gestation) born 2004-2010 with acute HS ≤28 days of life were identified, and clinical information was abstracted. Short-term outcomes were assessed via standardized neurological exam and rated using the Pediatric Stroke Outcome Measure (PSOM).

Results—Among 42 subjects, median gestational age was 39.7 weeks [interquartile range (IQR) 38-40.7 weeks]. Diagnosis occurred at a median of 1 day (IQR 0-7 days) after delivery. Twenty-seven (64%) had both intraparenchymal and intraventricular hemorrhage. Mechanism was hemorrhagic transformation of venous or arterial infarction in 22 (53%). Major risk factors included congenital heart disease (CHD), fetal distress, and hemostatic abnormalities. Common presentations included seizure, apnea, and poor feeding or vomiting. Acute hydrocephalus was common. Mortality was 12%. Follow-up occurred in 36/37 survivors at a median of 1 year (IQR 0.5-2.0). Among 17/36 survivors evaluated in stroke clinic, 47% demonstrated neurologic deficits. Deficits were mild (PSOM 0.5-1.5) in 9/36 (25%), and moderate-to-severe (PSOM ≥ 2.0) in 8/36 (22%).

Conclusions—In our cohort with acute HS, most presented with seizures, apnea, and/or poor feeding. Fetal distress and CHD were common. Nearly two-thirds had intraparenchymal with intraventricular hemorrhage. Over half were due to hemorrhagic transformation of infarction. Short-term neurologic deficits were present in 47% of survivors.

Keywords

neonatal; hemorrhagic stroke

INTRODUCTION

In newborns born prior to 32 weeks gestation, intraventricular hemorrhage is common and usually caused by germinal matrix hemorrhage. While less common in late preterm and term infants, hemorrhagic stroke (HS), defined as intraventricular, intraparenchymal or subarachnoid hemorrhage,[1] also occurs in this group. Much less is known about risk factors and outcome of HS in late preterm and term infants. Incidence of symptomatic HS in term infants has recently been estimated at 0.17/1000 live-births.[2-5]

Hemorrhage location often dictates the clinical course. Symptoms can include seizures or may be non-specific like apnea, respiratory distress, fever, or poor feeding.[6, 7] Significant neurodevelopmental impairment is a concern in late preterm and term neonates with symptomatic HS. Studies have reported impairment in 9% to 57%, though the higher estimate comes from a study that included infants with isolated subdural hemorrhage. Most studies report mortality rates from 1% to 25%.[6, 8]

Determining HS mechanism in late preterm or term neonates can be difficult. Some studies report an association between assisted deliveries and HS, but those results are not consistent.[9, 10] Fetal distress and postmaturity were recently shown to be independent risk factors for HS in neonates, but the mechanism of hemorrhage is unclear.[11] The presence of a bleeding diathesis increases the likelihood of HS, but these disorders are rare.[2] As neuroimaging modalities have become more sensitive, the likelihood of diagnosing more

subtle HS has increased.[12] More advanced neuroimaging may also provide insight into HS mechanism. We utilized our established prospective registry of childhood stroke to report risk factors, mechanism, and short-term outcomes of late preterm and term neonates with HS.

METHODS

Subjects

Subjects were identified from a prospective registry of childhood stroke at The Children's Hospital of Philadelphia enrolled 2004-2010. Stroke service consultation results in a standardized approach to classification and diagnosis of HS and is part of care for this condition at our institution. Consistent with the National Institute of Neurological Disorders and Stroke Common Data Elements definition (http://www.commondataelements.ninds.nih.gov/stroke.aspx#tab=Data_Standards, accessed 3/8/13), subjects were included if they were ≥34 weeks gestation, had HS that was intraparenchymal, intraventricular, or subarachnoid, and was diagnosed at ≤28 days of life.[1, 13] HS was confirmed with head CT or MRI. Subjects with isolated epidural or subdural hemorrhage were excluded since these entities are not considered HS.[1]

Clinical data

Clinical information was obtained by chart review. Presenting signs and symptoms, age at presentation, gestational age, delivery mechanism, and APGAR scores were recorded.[14] Fetal distress was defined as non-reassuring fetal heart tracings and/or decreased fetal movement prior to delivery. HS risk factors ascertained included presence of fetal distress, maternal factors like placental abruption, severe congenital heart disease (CHD), sepsis, extracorporeal membrane oxygenation (ECMO), or systemic anticoagulation.

Laboratory and radiologic evaluation

Laboratory values examined included complete blood count, lumbar puncture results, and coagulation and thrombophilia studies. A pediatric hematologist (CW) independently reviewed the hematology data. All acute and chronic (2 months-6 months post-event) neuroimaging including head computed tomography (HCT), magnetic resonance imaging (MRI), and magnetic resonance angiography and/or venography (MRA and MRV) was reviewed by a pediatric neuroradiologist (AV) who was blinded to the clinical interpretations and histories. Type and location of hemorrhage, parenchymal hemorrhage size, association with vascular thrombosis, and concurrent presence of subarachnoid and/or subdural hemorrhage were noted. Hemorrhagic transformation of arterial ischemic stroke was diagnosed when hemorrhage was within a significantly larger area of ischemia identified by restricted diffusion on MRI corresponding to an arterial territory. Venous infarcts were diagnosed when there was evidence of venous thrombosis and associated vasogenic and cytotoxic edema. In addition, presence of white matter changes, edema, hydrocephalus, watershed injury, and hypoxic ischemic injury were reported. HS mechanism was determined based on review of radiological and laboratory studies.

Outcome

Short-term outcomes included survival, hospitalization length, and neurological outcome assessed via the Pediatric Stroke Outcome Measure (PSOM) at the last stroke clinic evaluation. The PSOM is a validated outcome score for infants and children with stroke.[15, 16] Scores are assigned in five areas: right sensorimotor, left sensorimotor, expressive language, receptive language, and cognition/behavior. PSOM subscores are graded 0 (no deficit), 0.5 (mild deficit not interfering with function), 1 (moderate deficit

interfering with function), and 2 (severe deficit with loss of function). The total score ranges from 0 to 10. Follow-up data also included hemorrhage recurrence, hydrocephalus, and ventriculoperitoneal shunt placement. Utilization of rehabilitation services including physical, occupational, and speech therapy were noted as a proxy for neurodevelopmental impairment.

Statistics

Data were analyzed using Stata version 11.0 (College Station, TX). Categorical variables were summarized using frequencies and percentages. For continuous variables, data were summarized by the median with interquartile range (IQR).

The hospital institutional review board approved the study. Parental consent was obtained.

RESULTS

Subjects and risk factors

Forty-two subjects met inclusion criteria. Characteristics of the cohort, delivery information, HS risk factors, and presentations are summarized in Table 1. The majority of infants presented with symptoms within the first week of life. Most subjects were born full term via spontaneous vaginal delivery without use of assistive devices. Intrapartum or other head trauma was not recorded for any subject. The majority of cesarean sections were unplanned and performed due to fetal indications or labor arrest. APGAR scores were available in 31 subjects (74%). Median one and five minute APGAR scores were 8 (IQR 6-8) and 9 (IQR 8-9). While many subjects had several presenting symptoms, seizures were most common, affecting 27 (64%). In our cohort, severe CHD and fetal distress were the most common risk factors affecting 11 (26%) and 9 (21%) subjects, respectively. Diagnoses of neonates with severe CHD are listed in Table 2. Four of 11 subjects (36%) with severe CHD were diagnosed with HS prior to surgery. These 4 subjects were not on anticoagulation or ECMO prior to HS diagnosis.

Radiologic analysis

Table 3 lists radiologic features of the hemorrhagic strokes and stroke mechanism by radiographic review. A combination of intraventricular and intraparenchymal hemorrhage and presence of concomitant subdural and/or subarachnoid hemorrhages were prominent. While hydrocephalus was present on the acute scan in nearly half of subjects, only 4 required ventriculoperitoneal shunts. No subject had surgical evacuation of hemorrhage.

Thirty-five subjects (83%) had vascular imaging; 19 (45%) had both MRA and MRV, 10 (24%) had MRA only, 6 (14%) had MRV only. No vascular malformations were discovered among those with vascular imaging. More than half of subjects developed hemorrhage as a consequence of transformation of venous or arterial infarction. Germinal matrix and choroid plexus hemorrhage were also common. Despite systematic radiologic review, a hemorrhage mechanism could not be determined from the neuroimaging studies in 12 subjects (29%). Figure 1 demonstrates representative images.

Hematologic analysis

Overall 38% of subjects (16/42) had one or more hemostatic abnormalities at presentation. Table 4 delineates the hemostatic abnormalities in the 30 subjects with an identifiable hemorrhage mechanism on neuroimaging. For the remaining 12 subjects with no identified hemorrhage mechanism on neuroimaging, 50% (6/12) had severe hemostatic abnormalities that could result in intracranial hemorrhage. One subject had neonatal alloimmune thrombocytopenia with a nadir platelet count of 7×10^3/uL, 2 subjects were on ECMO with

associated thrombocytopenia and hypofibrinogenemia, and the remaining 3 subjects had severe disseminated intravascular coagulation. The other 6 subjects had a normal hemostatic evaluation. A prothrombotic evaluation was obtained in 90% (9/10) of the arterial ischemic stroke subjects and 75% (9/12) of the venous infarction subjects. The institutional standard prothrombotic evaluation includes factor V Leiden mutation, prothrombin gene mutation, anticardiolipin IgG/IgM, β2 glycoprotein IgG/IgM, dilute Russell viper venom time, protein C activity, protein S activity, antithrombin activity, homocysteine level, and lipoprotein (a). Only 1 subject with an arterial ischemic stroke had a prothrombotic abnormality (heterozygous for Factor V Leiden mutation).

Outcome

Median length of hospitalization was 13 days (IQR 8-24 days). Five subjects (12%) died when medical support was withdrawn due to poor prognosis. Thirty-six of 37 surviving subjects (97%) were evaluated at stroke clinic at median age of 1 year (IQR 0.5-2 years). Five (14%) had seizures during the follow-up period. Seventeen (47%) had a PSOM >0, indicating a neurologic deficit. Nine subjects (25%) had mild deficits (PSOM 0.5-1.5); 8 (22%) had a PSOM ≥2, indicating more severe deficits. At last follow-up, 56% were receiving physical, occupational, or speech therapy.

Follow-up imaging was performed at least 2 months after initial imaging in 15/37 survivors (41%; MRI 13, HCT 1, head ultrasound 1). No subject had recurrent hemorrhage. One infant with symptomatic intraventricular hemorrhage diagnosed on day of life 2 confirmed with MRI was found to have extensive asymptomatic superior sagittal sinus venous thrombosis on head ultrasound performed on day of life 12. This sagittal sinus thrombosis was not present on T1-weighted MRI at IVH diagnosis but was subsequently confirmed by MRI/MRV.

DISCUSSION

Few studies have evaluated risk factors and short-term outcomes of late preterm and term neonates with hemorrhagic stroke. In our cohort of 42 subjects, most HS was identified within the first week of life. The most common risk factors for HS included CHD and fetal distress. CHD has been demonstrated to be a risk factor for HS in infants previously.[17] Use of anticoagulation in this population likely contributed to HS in some. However, several neonates with CHD had HS prior to surgery or anticoagulation administration which suggests that the altered hemodynamics in neonates with severe CHD might predispose them to hemorrhage. Presence of fetal distress may be a proxy for prenatal pathologic changes like a compromised vascular environment that may predispose an infant to developing HS.[18, 19] Alternatively, fetal distress could be the first sign of fetal compromise due to in utero HS. Our findings were consistent with those of Armstrong-Wells and colleagues who identified fetal distress as a risk factor for perinatal HS in a population of over 300,000 neonates during a 10-year period.[11]

While other studies have shown an association between HS and assisted deliveries, most subjects in our cohort were born via spontaneous vaginal delivery without instrumentation.[6, 20] Furthermore, no subject had intrapartum or other head trauma indicating that intrapartum trauma is not a significant risk factor for HS in this population. Nearly one-third of subjects were born via unplanned cesarean section. In the case of unplanned cesarean sections in the absence of fetal distress, it is possible that subclinical compromise was present in the fetus.[21, 22]

The majority of subjects experienced hemorrhagic transformation of arterial or venous infarction. The most common location of HS was a combination of intraparenchymal and

IVH. Interestingly, nearly one-quarter of subjects in our cohort had more than one identified mechanism for hemorrhage, supporting the premise that HS in neonates may be multifactorial. In addition, we identified a subject who experienced an IVH followed by development of venous sinus thrombosis. The venous sinus thrombosis was not present on T1-weighted MRI at the time of initial IVH diagnosis. HS is a well-documented complication of cerebral venous sinus thrombosis.[23] A study by Wu et al demonstrated that 31% of term neonates with IVH also had a diagnosis of venous sinus thrombosis. Venous sinus thrombosis was postulated as the underlying cause of IVH.[12] Also, some IVH without obvious venous thrombosis could still be secondary to a medullary or cortical vein thrombosis that resolved prior to imaging. In our subject with IVH followed by venous thrombosis, although there was no definitive evidence that the thrombosis was caused by the IVH, the case suggests that increased intracranial pressure from hemorrhage could lead to venous stasis and thrombosis.

Hemostatic abnormalities were present in 38%. Many of these hemostatic changes, including low fibrinogen and platelet levels in those on ECMO, are potentially modifiable. Diagnosing and correcting coagulopathy may lead to decreased risk of HS. Preventing or treating coagulopathic changes in high-risk patients may help to decrease the risk of HS further.

Nearly half of survivors demonstrated a neurologic deficit at the last follow-up, and approximately 56% of subjects required physical, occupational, and/or speech therapy services. The frequency of neurologic deficits in our study was higher than in some studies, but lower than in others.[6, 8, 24] While more than half of survivors had normal neurologic function and deficits were often mild when present, 22% had moderate to severe deficits. Our assessment was not sensitive for deficits in language, cognition/behavior, or higher level motor skills given the young age of subjects at last assessment. Long-term follow-up is required to determine whether deficits emerge in these subjects with maturity.

Strengths of our study include prospective identification of HS in a consecutive cohort that was among the largest of this type. We had data from high quality imaging that was independently reviewed by a pediatric neuroradiologist, allowing for expert centralized and unbiased determination of the hemorrhage mechanism in the majority of subjects. In addition, we had data on short-term outcomes via a standardized neurological exam in 97% of surviving subjects and follow-up imaging at the same institution in many subjects, allowing for detection and systematic characterization of early neurologic deficits and recurrent hemorrhage.

Our study included patients for whom pediatric stroke consultation was obtained. Therefore, a potential limitation of our study was that ascertainment of neonatal HS in this cohort was possibly more narrowly defined than in some other studies. Differences in inclusion and exclusion criteria may affect the comparison of our findings to those of other published studies using different study eligibility criteria. For example, patients with hemorrhagic transformation of global hypoxic ischemic injury might be included in some outcome studies of neonatal cerebral hemorrhage but were excluded from our series because this condition is not included in the definition of HS.[1] Another limitation is that this is a single-center study with a large CHD program. Therefore, our cohort may over-represent the role of CHD as a risk factor compared to the general population of newborns with HS. It is likely that neurologic deficits at follow-up in this subgroup of the cohort are attributable in part to their underlying heart disease, in addition to the direct effects of HS. Therefore, outcome data from a cohort like ours which includes a large number of children with CHD may be skewed by CHD subjects' outcomes. Our sample size was insufficient to separately analyze outcome by risk factor group.

CONCLUSIONS

Risk factors for hemorrhagic stroke in late preterm and term infants included severe congenital heart disease and fetal distress. Mechanism was hemorrhagic transformation of arterial or venous infarction in more than half and choroid plexus or germinal matrix hemorrhage in more than one-third of subjects. At short-term follow-up, no recurrent hemorrhage occurred, but nearly half of survivors had neurologic deficits. Long-term follow-up is needed to characterize the presence and severity of neurologic deficits as the children mature.

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What is already known on this topic Symptomatic hemorrhagic stroke has been described in term and late preterm infants, though few studies have examined risk factors and outcome in this age group.

What this study adds Hemorrhagic transformation of infarction was the leading mechanism of HS. Germinal matrix and choroid plexus hemorrhage were common in term and late preterm infants with HS. Neurologic deficits or death occurred in more than 50%.

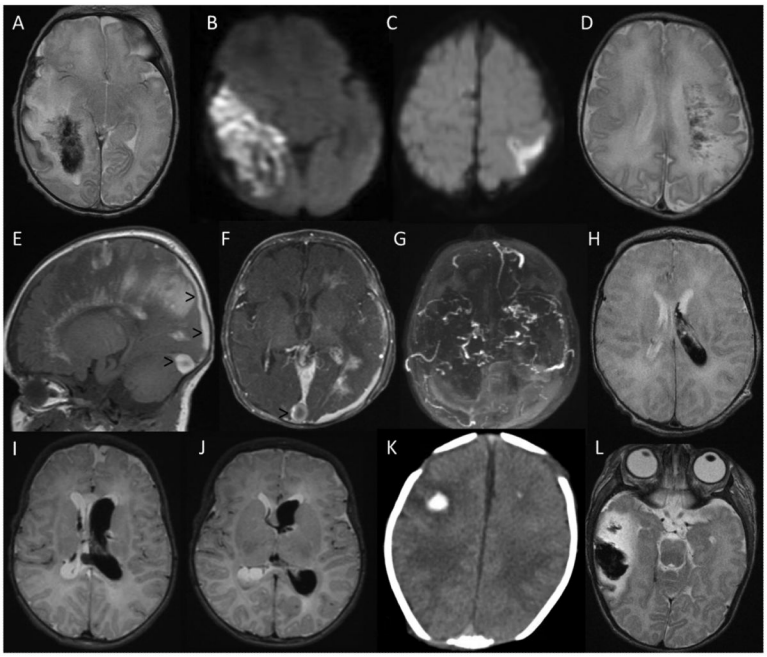

Figure 1.

Imaging from subjects with hemorrhagic stroke: arterial ischemic stroke (A,B), watershed territory infarct (C), medullary vein thrombosis (D), cerebral venous sinus thrombosis (E-G; > demonstrates thrombus), intraventricular hemorrhage due to choroid plexus hemorrhage (H), intraventricular hemorrhage due to germinal matrix hemorrhage (I,J), extracorporeal membrane oxygenation (K), and hemorrhage of undetermined mechanism (L).

Table 1

Subject characteristics (total N=42), hemorrhagic stroke risk factors, and clinical presentations

Demographics/Delivery Information	
Median gestational age (IQR)	39.7wks (38-40.7 weeks)
Median age at presentation (IQR)	1 day (0-7 days)
Male	21 (50%)
SVD without instrumentation	26 (62%)
SVD with instrumentation	4 (10%)
Unscheduled C-section	12 (29%)
Caesarean section with instrumentation	1 (2%)
Median APGAR* with IQR, 1 min, 5 min	8 (6-8) and 9 (8-9)
Clinical presentation	
Seizure	27 (64%)
Apnea	12 (29%)
Poor PO/vomiting	12 (29%)
Fever	6 (14%)
Bulging fontanel	4 (10%)
Irritability	4 (10%)
Risk factors for hemorrhage	
Severe congenital heart disease	11 (26%)
Fetal distress	9 (21%)
ECMO	4 (10%)
Sepsis	1 (2%)
Placental abruption	0 (0%)
None identified	25 (60%)

N, number; IQR, interquartile range; SVD, spontaneous vaginal delivery;

*APGARs available in 31 subjects; min, minutes; ECMO, extracorporeal membrane oxygenation; PO, oral intake

Table 2

Severe congenital heart disease subjects

Subject number	Congenital heart disease	Surgery type days to HS diagnosis	ECMO/ anticoagulation
#2	Coarctation of aorta, hypoplastic L-aorta	No surgery prior to HS diagnosis	None
#5	Hypoplastic left heart	POD 5, cardiac surgery with bypass; POD 4, ECMO canalization, POD 0, ECMO decannulation with carotid ligation and jugular repair	ECMO
#10	Pulmonic stenosis	POD 0, cardiac catheterization without heparin	None
#13	Total anomalous pulmonary venous return	POD 1, cardiac surgery with bypass, POD 0, chest/sternal closure	None
#14	Tetralogy of fallot, pulmonary atresia	No cardiac surgery prior to HS diagnosis, POD 0, ligation of tracheo-esophageal fistula and repair esophageal atresia,	None
#19	L-transposition of the great arteries, Ebstein's Anomaly	POD 7, cardiac repair with bypass	Heparin drip
#25	Transposition of the great arteries, atrioventricular canal, severe atrioventricular valve regurgitation, pulmonic stenosis	No cardiac surgery prior to HS diagnosis	None
#29	Double outlet right ventricle, pulmonic stenosis, patent foramen ovale, small patent ductus arteriosis	POD 2, cardiac repair with bypass and ECMO canalization	ECMO
#38	Common atrioventricular canal, tetralogy of Fallot	No cardiac surgery prior to HS diagnosis	None
#41	Double outlet right ventricle, pulmonary atresia, ventricular septal defect	POD 14, cardiac surgery with bypass	None
#42	Hypoplastic left heart	POD 2, cardiac surgery with bypass and ECMO canalization	ECMO

#, unique subject number identical to those used in Table 3; HS, hemorrhagic stroke; ECMO, extracorporeal membrane oxygenation; POD, post-operative day

Table 3

Radiological features of hemorrhagic stroke and stroke mechanism by radiographic review

Hemorrhage location	**N, (%)**
Isolated intraparenchymal hemorrhage (IPH)	11 (26%)
Isolated intraventricular hemorrhage (IVH)	4 (10%)
IPH+IVH	27 (64%)
Size of intraparenchymal hemorrhage	
Maximal dimension <1 cm	13 (31%)
Maximal dimension 1-3 cm	17 (40%)
Maximal dimension >3cm	8 (19%)
Subarachnoid hemorrhage present	25 (60%)
Subdural hemorrhage present	3 0 (71%)
Periventricular hemorrhage present	18 (43%)
Hydrocephalus on acute scan	19 (45%)
Borderline	9 (21%)
Moderate-severe	10 (24%)

Hemorrhagic stroke mechanism	**N, (%)**
Hemorrhagic transformation of arterial ischemic stroke	10 (24%)
Hemorrhagic transformation of venous infarction	12 (29%)
Cerebral venous sinus thrombosis	*5 (12%)*
Isolated medullary vein thrombosis	*7 (17%)*
Hemorrhagic transformation of arterial watershed injury	2 (5%)
Choroid plexus hemorrhage	8 (19%)
Germinal matrix hemorrhage	8 (19%)
Unknown	12 (29%)
Number of subjects with radiographic evidence of > 1 mechanism of hemorrhage	10 (24%)

N, number

Table 4

Hemostatic abnormalities in the 30 subjects with hemorrhagic stroke mechanism identified on neuroimaging

	Arterial ischemic stroke	Venous infarction	Watershed infarction	Choroid plexus / germinal matrix
Total Subjects	10	12	2	15
Subjects with >1 neuroimaging category N (%)	4 (40)	5 (41.7)	2 (100)	6 (40)
Hemostatic abnormalities N (%)	2 (20)	4 (33.3)	0	5 (33.3)
Platelet Count ($\times 10^3$/uL)				
100-150	--	--	--	#14
50-100	--	#11, 38, 29	--	#19, 38
<50	--	#25	--	#25, 42
Prolonged PT/PTT or ACT	--	#25, 38	--	#25, 38, 42
Fibrinogen (mg/dL)				
100-150	#2	--	--	--
50-100	--	#11	--	#42
<50	--	--	--	--
Heparin exposure (ECMO or CPB)	--	#29	--	#42
Congenital bleeding disorder	#15 (Type 1 VWD)	--	--	--

N, number; #, unique subject number; PT, prothrombin time; PTT, partial thromboplastin time; ACT, activated clotting time;

ECMO, extracorporeal membrane oxygenation; CPB, cardiopulmonary bypass; VWD, von Willebrand disease. Note: Subjects with more than one mechanism of injury were included in each category that applied.