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Blunt Trauma as a Risk Factor for Group A Streptococcal Necrotizing Fasciitis

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Abstract

Purpose—Anecdotal reports suggest that blunt trauma and seemingly innocuous musculoskeletal injuries (*e.g.* muscle strains) are risk factors for developing necrotizing fasciitis (NF) and myositis caused by group A *Streptococcus* and other bacteria; however, this hypothesis has not been tested in analytic epidemiologic studies of invasive group A streptococcal (GAS) disease. We conducted two case-control studies to determine whether nonpenetrating trauma is a risk factor for either NF or severe cellulitis caused by GAS.

Methods—A secondary analysis of patients that were hospitalized throughout Florida for invasive GAS disease during a four-year period was conducted. Two case series were used. The first series comprised patients who had severe GAS cellulitis. The second were patients who had GAS NF. Cases were compared to a single control series comprised of patients with invasive GAS disease not including either NF or cellulitis (*e.g.* primary bacteremia, septic arthritis, *etc.*).

Results—After adjusting for age, race, and clindamycin, GAS NF cases were 5.97 times as likely as controls to have a recent history of blunt trauma ($p=0.04$). Patients with severe cellulitis were not more likely than controls to have associated blunt trauma.

Conclusions—Nonpenetrating trauma is significantly associated with the development of GAS NF.

Keywords

Streptococcus pyogenes; necrotizing fasciitis; wounds, nonpenetrating; cellulitis

Invasive disease caused by group A *Streptococcus* (GAS; *S. pyogenes*) poses a major public health problem in the United States. Nationwide, it is estimated that over 11,000 cases of invasive GAS infections occur each year, an incidence six times the annual reported rate of meningococcal disease (1). Though most infections caused by GAS are of the non-invasive variety (e.g. pharyngitis), one of the more dramatic (and lethal) presentations is that of necrotizing skin and soft tissue infections, including necrotizing fasciitis (NF) and myositis. The popular press has dubbed GAS the “flesh-eating” bacterium in light of these latter manifestations. Though the case-fatality rate of GAS NF is 20% (2), mortality rates nearing 70% occur when streptococcal toxic shock syndrome complicates the disease (3).

Anecdotal reports suggest that blunt trauma and seemingly innocuous musculoskeletal injuries (e.g. muscle strains) are risk factors for developing NF and myositis caused by GAS and other bacteria (4-7); however, this hypothesis has not been tested in analytic epidemiologic studies of invasive GAS disease (8, 9). The biological plausibility of this hypothesis was recently elucidated by Bryant *et al.* (10), who discovered that minor nonpenetrating injury increases the production of a GAS-binding protein (vimentin) on the surface of injured skeletal muscle, possibly facilitating the initiation of GAS infection. These interesting findings provide a molecular basis for explaining the development of severe soft-tissue infections caused by GAS at the site of prior muscle trauma. Therefore, we conducted a case-control study using data from a previous investigation (11) of invasive GAS disease to test the hypothesis that blunt trauma is a risk factor for GAS NF. To determine whether blunt trauma was uniquely a risk factor for NF as opposed to cellulitis, we also conducted a case-control study using patients with severe GAS cellulitis.

Materials and Methods

Patient Population

We conducted a secondary analysis of a retrospective study conducted in Florida, the methods of which were described in detail elsewhere (11). Briefly, the original study population was comprised of 257 patients who were hospitalized throughout the state of Florida between August 1996 and August 2000 for invasive GAS disease and reported to the Florida Department of Health (Tallahassee, Florida). Invasive GAS disease was defined as isolation of group A *Streptococcus* from a normally-sterile site or isolation from a nonsterile site in a patient with NF.

Surveillance data were obtained from the Florida Department of Health and consisted of demographic and clinical data on these patients. To clarify, for each case of invasive GAS disease that was reported by a county health department to the Florida Department of Health, a three-page case report form was completed after review of the patient’s medical record. This chart review was usually performed by an epidemiology staff member at the reporting county health department. The surveillance case report form contained a section entitled, “Underlying illness or prodrome” which captured a history of blunt trauma via a check box (12). Another section required the chart reviewer to check off the diseases caused by GAS including NF and cellulitis. The cellulitis check box was combined with abscess (“cellulitis/abscess”) on our form. The need for surgical debridement or incision and drainage was also recorded on each case report form. There were 37 patients in the current

sample with documented NF. Eighteen of these patients were also given the diagnosis of cellulitis. The latter group of patients was included in the NF cases for our analyses.

Cases of cellulitis (not including patients with NF; $n = 63$) were classified as severe on the basis that (a) the patients required hospitalization and (b) all had at least one culture positive for GAS from a normally sterile site, such as the bloodstream (62 of the 63 or 98.4% were bacteremic). For the present analysis we did not have primary medical records and therefore were unable to validate the diagnosis of NF. Cultures that were positive for GAS (*e.g.* blood, body fluids, and wounds) were recorded on the case report forms.

Analyses of this database were approved by the Institutional Review Board of the Texas Tech University Health Sciences Center School of Medicine at El Paso.

Statistical Analysis

The data were analyzed using logistic regression. The exposure of interest was blunt trauma (present or absent). Two case-control studies were performed using the same control group. The first group of cases was patients who had GAS cellulitis noted on their case report form. The second series of cases were patients who had GAS NF. Controls were identified from the same dataset as the cases. The series of controls were patients who were not only free of NF but also were free of cellulitis.

The change-in-estimate method (13) was used to determine if the following variables were confounders of the association under study: age (a continuous variable), race (Caucasian vs Other race), sex, the presence of diabetes (yes/no), and receipt of the antibiotic clindamycin during the hospital stay (yes/no). Clindamycin was evaluated for confounding because of its potential to alter the risk of developing GAS NF by suppressing the production of streptococcal pyrogenic exotoxins known as superantigens (14). GAS superantigens are believed to play a role in the development of GAS NF (14). The change-in-estimate method, unlike forward selection or backward elimination, does not rely on *p*-values to choose covariates for inclusion in the final model. This technique, rather, relies on a change in the blunt trauma odds ratio (OR) when one or more potential confounders are added to the model (13). We used a 10% change to build our model. Crude and adjusted ORs are presented along with *p*-values and 95 percent confidence intervals. A total of 211 records were available for logistic regression.

Results

Caucasians comprised a greater proportion of the GAS NF cases than the control series (Table 1). The prevalence of blunt trauma was higher among the GAS NF cases than the controls (10.8% versus 3.6%) (Table 1). This large disparity was not seen when the GAS cellulitis patients were the cases of interest. The prevalence of blunt trauma in this group was 4.8%.

Unadjusted and adjusted ORs quantifying the association between a history of blunt trauma and the two skin and soft-tissue outcomes are shown in Tables 2 and 3. All of the ORs reported in Table 2 are elevated; however, none are statistically significant. After adjusting

for age, race, and receipt of clindamycin during the hospital stay, GAS NF cases were approximately six times as likely as controls to have blunt trauma listed on their case report form as a predisposing factor (Table 3): Adjusted OR=5.97, $p=0.04$. The crude and adjusted ORs for GAS cellulitis associated with a recent history of blunt trauma (Table 2) were lower than the respective ORs for NF (Table 3).

It is a possibility that a proportion of the patients classified as GAS cellulitis cases may not have had cellulitis but rather abscesses. Of the 63 patients diagnosed with cellulitis/abscess, 21 underwent a surgical debridement procedure, suggesting the presence of a soft tissue abscess. When these patients were excluded from analysis, blunt trauma remained unassociated with cellulitis ($n=42$): OR=0.0, $p=0.27$.

Discussion

Clinicians have noted a possible link between blunt trauma (and muscle strains) and NF for several years (4-7). To this body of anecdotal evidence, we add data from a controlled epidemiologic study. We found a statistically significant association between blunt trauma and GAS NF among patients hospitalized throughout Florida for invasive GAS disease who were reported to the Florida Department of Health. Interestingly, we failed to detect a significant association between blunt trauma and severe GAS cellulitis. The discrepant association of nonpenetrating trauma with NF but not with cellulitis could reflect key differences in the pathogenesis of these distinct clinical entities. Alternatively, our study may have been underpowered to detect this association.

Both cellulitis and NF can follow the direct inoculation of the sub-epidermal soft tissues when a breach in skin integrity occurs, for example as a result of penetrating trauma or fissured skin. Thus, the exogenous seeding of the soft tissues is a shared risk factor for these two conditions. However, GAS is also capable of seeding the skin and soft tissues through hematological dissemination. It is through this mechanism that blunt (nonpenetrating) trauma likely poses a risk for necrotizing soft tissue infections. However, the reasons why blunt trauma might predispose to NF and/or myonecrosis but not cellulitis remain unclear. Perhaps the blunt trauma associated with muscle and/or fascial necrosis must be of sufficient severity to damage underlying skeletal muscle. As Bryant *et al.* recently postulated in their work defining the intermediate filament protein vimentin as a major skeletal-muscle GAS-binding protein (10), between one and two days after acute injury, “regenerating muscle cells and infiltrating immature muscle-cell precursors maximally express vimentin on their surface, mediating the focal adhesion of GAS in sufficient numbers to initiate infection (10).” The pathogenesis of cellulitis by blood-borne GAS is incompletely understood, but may not require the binding of GAS to vimentin-expressing cells.

We detected negative confounding (confounding towards the null value) when GAS NF was the outcome of interest (Table 2 3). We did not consider the use of nonsteroidal anti-inflammatory drugs as a potential confounder since we did not have complete data regarding the timing, dose, and indication for nonsteroidal anti-inflammatory drug use. Furthermore, this class of medications has not been found to increase the risk for the development of GAS NF (15).

A limitation of this study was the inability to validate the diagnosis of NF found on the invasive GAS disease surveillance forms. We did not have access to the medical records of these hospitalized patients. However, if patients with blunt trauma were just as likely to have their outcomes misclassified as patients with a negative blunt trauma history, then nondifferential (random) misclassification would be present.

Random misclassification would most likely have biased the OR towards the null value of one (the value of no association) (16). Correcting for this bias would result in an even stronger OR (*i.e.* > 5.97). Furthermore, the forms were completed by professionals with clinical and/or public health training and included county health department epidemiologists, county health department public health nurses, and hospital infection control practitioners.

We chose to include the 18 patients with the combined diagnoses of cellulitis and NF in the group of NF cases used in our analyses. We assumed that these diagnoses were referring to the same lesion(s) in individual patients, though this could not be confirmed. Certainly early NF, before overt signs or symptoms of underlying necrosis emerge, can be misdiagnosed as cellulitis (14).

One weakness of this study was the inability to accurately discriminate between cellulitis with or without an enclosed fluid collection (abscess). However, when excluding patients who required surgical debridement (n=42) we confirmed the absence of association between cellulitis and blunt force injury: None of the 42 cases had a history of blunt trauma.

Another limitation of this study is the possibility that ascertainment bias affected the perceived relationship between blunt trauma and NF. Patients with GAS NF may have been more likely to have been questioned about antecedent trauma and have this information noted in their medical record than patients with other manifestations of invasive GAS disease. This issue underscores the importance of validating our findings in a prospective study of GAS NF. A prospective design would also allow the control of penetrating trauma, a potential confounder.

To our knowledge, this is the only case-control study to report a statistically significant association between blunt trauma and the outcome of GAS NF. The relationship between nonpenetrating trauma and invasive GAS infection begs the question of whether blunt trauma victims should be assessed for asymptomatic nasopharyngeal carriage (*e.g.* by rapid streptococcal antigen testing and/or culturing) and treated with antibiotics if positive. A study to assess the impact of this approach would have to be prohibitively large given the rarity of this association. Furthermore, the number needed to screen and treat to prevent a single invasive GAS infection would likely be very large and thus not cost effective. Nonetheless, given the frequent nature of muscle strains and blunt trauma (17), further laboratory and epidemiologic investigations to elucidate the causal mechanisms of GAS NF are warranted.

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Table 1

Clinical and Demographic Characteristics of 211 Patients Hospitalized for Invasive Group A Streptococcal Disease

	GAS Cellulitis Cases[*] (n=63)	GAS NF Cases (n=37)	Controls[†] (n=111)
Clinical variables			
Blunt trauma, n (%)	3 (4.8)	4 (10.8)	4 (3.6)
Clindamycin, n (%)	20 (31.8)	25 (67.6)	24 (21.6)
Diabetic, n (%)	15 (23.8)	7 (18.9)	15 (13.5)
Demographic variables			
Caucasian, n (%)	48 (76.2)	34 (91.9)	85 (76.6)
Male, n (%)	32 (50.8)	18 (48.7)	57 (51.4)
Median age (range)	56 y (0.7 y – 98 y)	63 y (4 y – 103 y)	52 y (0.1 y – 95 y)

Note: GAS=group A streptococcal, NF=necrotizing fasciitis, y=years.

* Patients with invasive GAS disease who do not have NF.

† Patients with invasive GAS disease free of NF and cellulitis.

Table 2

Unadjusted and Adjusted Odds Ratios (OR) for Group A Streptococcal Cellulitis among Patients Hospitalized for Invasive Group A Streptococcal Disease (n=174)

Potential Risk Factor	Unadjusted			Adjusted*		
	OR	95% Confidence Interval	P-value	OR	95% Confidence Interval	P-value
Recent blunt trauma?						
Yes	1.34	0.29-6.18	0.71	1.29	0.26-6.29	0.75
No	1	(Referent)	--	1	(Referent)	--
Age (10 year increase)	1.11	0.97-1.27	0.11	1.13	0.99-1.30	0.07
Received clindamycin?						
Yes	1.69	0.84-3.39	0.14	1.82	0.88-3.73	0.10
No	1	(Referent)	--	1	(Referent)	--

* Each odds ratio is adjusted for the remaining variables in the table.

Table 3

Unadjusted and Adjusted Odds Ratios (OR) for Group A Streptococcal Necrotizing Fasciitis among Patients Hospitalized for Invasive Group A Streptococcal Disease (n=148)

Potential Risk Factor	Unadjusted			Adjusted*		
	OR	95% Confidence Interval	P-value	OR	95% Confidence Interval	P-value
Recent blunt trauma?						
Yes	3.24	0.77-13.68	0.11	5.97	1.04-34.16	0.04
No	1	(Referent)	--	1	(Referent)	--
Age (10 year increase)	1.17	1.00-1.37	0.054	1.20	1.00-1.45	0.053
Race						
White	3.47	0.98-12.21	0.053	2.76	0.67-11.41	0.16
Other	1	(Referent)	--	1	(Referent)	--
Received clindamycin?						
Yes	7.55	3.32-17.20	< 0.0001	7.70	3.22-18.44	< 0.0001
No	1	(Referent)	--	1	(Referent)	--

* Each odds ratio is adjusted for the remaining variables in the table.