Kallikrein-Kinin System Activation in Streptococcal Toxic Shock Syndrome

A retrospective analysis of 7 patients with streptococcal toxic shock revealed isolated prolongation of the activated partial thromboplastin time, which returned to normal during recovery. Levels of factor XII were reduced in 2 patients who had single factor assays performed, consistent with activation of the kallikrein-kinin system. We speculate that bradykinin release following activation of the kallikrein-kinin system in streptococcal toxic shock may underlie the features of pain, capillary leaking, and severe hypotension characteristic of this syndrome.

Shock due to invasive *Streptococcus pyogenes* infection is characterized by hypotension, edema, erythema, and myalgia. The pathophysiology of streptococcal toxic shock syndrome (STSS) has been attributed in part to the proinflammatory effects of T cell–derived cytokines produced in response to streptococcal superantigens [1]. However, STSS can result from infection with strains that have little detectable superantigenic activity, which suggests that additional pathophysiological processes may account for STSS. Bradykinin is a host-derived nonapeptide released by the kallikrein-mediated cleavage of kininogen during contact activation and is known to cause pain, edema, and hypotension [2]; it is attractive to speculate that contact system activation might contribute to the features of STSS.

Two of our patients with STSS had markedly prolonged activated partial thromboplastin times (APTTs, intrinsic pathway). Prothrombin times (PTs, extrinsic pathway) were normal, and the patients did not have disseminated intravascular coagulation (DIC). Further tests revealed that levels of factor XII, but not other components of the intrinsic pathway, were reduced in both patients (0.29 units/mL and 0.17 units/mL; normal range, 0.5–1.5 units/mL). The pattern of abnormalities suggested activation of the contact system. We therefore undertook a small retrospective case record study of coagulation findings for patients who had STSS and compared results with findings for patients who were hospitalized with group A streptococcal infection without STSS (GAS) and for patients who had bacteremia due to other infections (NGAS).

All patients with group A streptococcal infection who were hospitalized from January 1992 through May 1998 were identified (20 patients); archived records were obtained for each patient, in accordance with institutional and Royal College of Physicians guidelines for research concerning patient case records. Those patients with STSS were identified by standard criteria [1]. A control group of 40 patients with bacteremia due to organisms other than *S. pyogenes* who were hospitalized from May 1997 through September 1997 was similarly identified. Patients were then excluded from the study if they had not undergone coagulation studies at admission, if they were receiving anticoagulant therapy, or if they had leukemia. Prolongation of APTT was

![Figure 1](image-url)

**Figure 1.** A. Prolongation of activated partial thromboplastin time (APTT) in 7 patients with streptococcal toxic shock syndrome (STSS), 8 patients with group A streptococcal infection but no STSS who were hospitalized (GAS), and 18 patients with bacteremia due to other infections (NGAS). Horizontal dashed line indicates upper limit of normal range for APTT. Differences between values for STSS patients and values for either GAS or NGAS patients are significant (*P* = .0009, Kruskal-Wallis test; *P* = .002 for pairwise comparison). B. Change in APTT prolongation during treatment for STSS in 4 patients.
calculated from the number of seconds between patient APTT and the upper limit of the quoted normal range. For patients with prolonged APTT, sequential data were collected.

There were no differences in PTs between STSS, GAS, and NGAS patients who met the inclusion criteria. Two of 7 STSS patients and 2 of 18 NGAS patients had DIC, and PTs were prolonged only in these patients. In contrast, APTTs were prolonged in 7 of 7 STSS patients compared with 1 of 8 GAS patients and 4 of 18 NGAS patients (figure 1A). Sequential coagulation data were available for 4 of 7 STSS patients; these data showed that the abnormalities in APTT returned to normal over time (figure 1B).

Although 2 STSS patients had DIC, all the remaining STSS patients had isolated APTT prolongation, a feature that was not seen in GAS or NGAS patients. Isolated prolongation of APTT is often ignored in the clinical setting, unless hemophilia or lupus anticoagulant disease is suspected. It is of course possible that a similar pattern of coagulation abnormality occurs in other forms of septic shock; by definition, all 7 of the STSS patients in our small study had shock.

Contact activation has been documented in cases of sepsis due to gram-negative organisms [3, 4] but rarely in cases of infection due to gram-positive organisms [5, 6]. To our knowledge, isolated prolongation of APTT has not been previously reported. None of our patients with isolated prolongation of APTT had a bleeding tendency, in contrast to those with DIC. Contact activation in STSS might be initiated through an interaction between streptococcal surface components, such as M protein or peptidoglycan, and host contact factors [7, 8] or by proteolytic cleavage of contact components by secreted bacterial products, such as streptococcal cysteine protease or streptokinase [9, 10]. The hypothesis that contact activation leads to bradykinin release could explain several key features of STSS; it is possible that therapeutic inhibition of this pathway using inhibitors of contact factors or bradykinin antagonists may decrease mortality in patients with severe STSS.

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Neurological Symptoms during Primary Human Immunodeficiency Virus (HIV) Infection Correlate with High Levels of HIV RNA in Cerebrospinal Fluid

This analysis involves 22 patients with diagnosed symptomatic human immunodeficiency virus (HIV) infection. Neurologic symptoms were present in 11 patients, ranging from severe and persistent headache to clinical signs suggestive of meningitis. A strong correlation between neurological symptoms and cerebrospinal fluid (CSF) viral load was found. The mean CSF HIV ribonucleic acid (RNA) level was 4.12 log for patients with neurological symptoms and 2.58 log for patients without neurological symptoms ($P < .00001$). Plasma viral load alone does not correlate or predict central nervous system (CNS) involvement. In our sample of patients, HIV RNA levels could be detected in most patients regardless of the presence of neurological symptoms. Moreover, early treatment including drugs with high levels of penetration in the CNS must be considered for patients with primary HIV infection.

Symptoms of the acute retroviral syndrome (ARS) have been

References


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