Streptococcus associated toxic shock

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Abstract
In the past few years, there appears to have been a change in the spectrum of disease caused by group A β-haemolytic streptococcus (GABHS), and a toxic shock-like syndrome caused by this organism has recently been described in adults. We report four children with an acute illness characterised by rapid progression of shock, erythematous rash, multisystem organ involvement, electrolyte derangements, and desquamation who fulfil the previously established diagnostic criteria for toxic shock syndrome. Three of the children had extensive cutaneous and soft tissue infection and the fourth had peritonitis. All four developed bacteraemia. Treatment included aggressive cardiovascular resuscitation and antibiotic therapy. Although no patient died, they suffered multiple and severe complications requiring prolonged treatment and hospitalisation. Streptococcal toxic shock syndrome is a separate and clearly defined entity occurring in previously healthy children.

In 1978, Todd and Fishaut described seven children with an acute disease characterised by fever, mucous membrane hyperaemia, subcutaneous oedema, desquamating erythroderma and rapid progression to hypotension and multisystem organ involvement, and which they called staphylococcal toxic shock syndrome. The disorder subsequently became more widely recognised as an illness affecting young women, which was associated with vaginal colonisation by Staphylococcus aureus and the use of tampons. At least 13% of cases are not associated with menstruation but with focal staphylococcal infections and/or colonisation, and a significant proportion of these non-menstrual cases are children.

In the past decade, major advances have occurred in the understanding of the pathogenesis of staphylococcal toxic shock syndrome. It is now well established that most cases are caused by a number of related enterotoxins produced by S aureus, the most common of which is the 22 kDa protein called toxic shock syndrome toxin-1 (TSST-1). TSST-1 and other enterotoxins are thought to cause the disorder by activating host inflammatory responses, and in particular by triggering release of cytokines. In the past four years, there have been a number of reports of a toxic shock-like disorder occurring in both adults and children, which has been associated not with S aureus but with group A β-haemolytic streptococcus (GABHS). Furthermore, there appears to have been an increase in the prevalence of serious invasive disease due to GABHS in many parts of the world.

In order to illustrate the clinical and pathological features of the disease, we report four children with streptococcal associated toxic shock syndrome and discuss the mechanisms involved in its pathogenesis.

Patients and methods
Streptococcus associated toxic shock syndrome was diagnosed in four children between February 1988 and November 1990. Three were admitted to the Hospital for Sick Children, Great Ormond Street, London, and one to Guy's Hospital, London (table 1). All four cases fulfilled the diagnostic criteria for staphylococcal toxic shock syndrome, but in each case GABHS was isolated from the blood (table 2).

Table 1 Clinical characteristics of four children with streptococcus associated toxic shock syndrome

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical presentation</th>
<th>Initial symptoms</th>
<th>Prodromal period</th>
<th>GABHS isolation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 years</td>
<td>F</td>
<td>Shock, fascitis</td>
<td>Fever, rash</td>
<td>6 days</td>
<td>Blood, skin wound</td>
</tr>
<tr>
<td>2</td>
<td>22 months</td>
<td>F</td>
<td>Shock, cellulitis</td>
<td>Fever, focal swelling</td>
<td>12 hours</td>
<td>Blood, bullae, nose, skin</td>
</tr>
<tr>
<td>3</td>
<td>13 days</td>
<td>F</td>
<td>Peritonitis, shock</td>
<td>Diarrhoea, rash</td>
<td>3 days</td>
<td>Blood, nose, peritoneal fluid</td>
</tr>
<tr>
<td>4</td>
<td>10 weeks</td>
<td>F</td>
<td>Shock, cellulitis</td>
<td>Fever, focal swelling</td>
<td>18 hours</td>
<td>Blood</td>
</tr>
</tbody>
</table>

*From onset of symptoms to shock.
GABHS, Group A β haemolytic streptococci.
Microorganisms were recovered and identified according to standard procedures. Antibiotic susceptibility was determined by the disc diffusion method in the microbiological laboratories of the respective hospitals.

CASE REPORTS

Case 1
A previously healthy 10 year old girl experienced pain and swelling over both ankles three days after sustaining a cut below her left knee. She subsequently developed a non-specific macular erythematous rash and fever and was admitted to a local hospital. During the ensuing five days, she became increasingly tachycardic and jaundiced, and blistering areas were noted in the right upper limb.

After 24 hours of progressive drowsiness and hypotension she was transferred to Guy’s Hospital where, on arrival, she was toxic and leathargic but responsive. Her temperature was 39°C, heart rate 150 beats/min, respiratory rate 40/min, and systolic blood pressure 85 mm Hg. She had red lips and tongue with conjunctival hyperaemia and mild icterus. A soft 2/6 systolic murmur was noted. The liver was 2 cm below the right costal margin. Her ankles and wrists were intensely swollen. A fine papular generalised rash with desquamation, particularly over the trunk and limbs, was found in conjunction with large yellow blisters and necrotic areas over her right forearm and lateral aspect of her left foot. The pulse in the right radial artery was absent, though detectable on Doppler examination. Initial investigations were as follows: haemoglobin concentration 87 g/l, white cell count 30×10⁹/l with 25×10⁹ neutrophils, platelet count 251×10⁹/l, and erythrocyte sedimentation rate 45 mm/hour. Biochemical findings showed concentrations of sodium 125 mmol/l, urea 22.4 mmol/l, creatinine 175 μmol/l, bilirubin 71 mmol/l and albumin 31 g/l, creatine phosphokinase 3108 U/l and aspartate aminotransferase 181 U/l. Urine contained granular casts and blood cells, and was positive for myoglobin and protein (3+), urinary sodium was less than 10 mmol/l. Blood cultures and swabs from the cut below the left knee grew GAS.

She was resuscitated with large volumes of colloid and required inotropic support with dobutamine and dopamine. Despite an adequate central venous pressure, she remained poorly perfused; a continuous infusion of prostacyclin was introduced as a vasodilator. She was electrically ventilated and required full sedation and paralyzation. High dose penicillin and fluoroquinolone were started. Her oxygen requirement increased over the next few hours and radiological changes consistent with adult respiratory distress syndrome appeared. After resuscitation, her renal and hepatic function showed improvement.

Swelling of the soft tissues over her right wrist and elbow joints became more noticeable. As she was weaned off muscle relaxant drugs, a compartment compression syndrome was diagnosed in her right forearm and in both legs. Fasciectomy was carried out in all affected limbs and yellow fluid drained from the fasciae. In spite of the decompression of her forearm, the muscles looked progressively less viable over the next few days. A bone scan suggested an avascular right ulna. Antibiotic therapy was changed to cefotaxime and clindamycin. Sensation of the right hand disappeared, and three weeks after admission, amputation of the right upper limb below the elbow was carried out. Additional amputation of her feet was avoided, although extensive skin grafting was necessary. Progressive clinical recovery followed with re-establishment of normal renal, hepatic, and pulmonary function. She returned to the local hospital five weeks after initial admission.

Case 2
A 22 month old girl presented to a local hospital with a one week history of cough, fever, and mild facial swelling. One day before admission, she developed multiple red bullae over her trunk and limbs. On admission, she was febrile (40-6°C), with a rate of 200 beats/min, and blood pressure of 65/40 mm Hg. She had generalised subcutaneous oedema and delayed peripheral perfusion. A presumptive diagnosis of septic shock was made and aggressive fluid resuscitation (in excess of 300 ml/kg) was instituted. Initial antimicrobial therapy included clindamycin, fusidic acid and gentamicin. Laboratory investigations recorded haemoglobin concentration 82 g/l, white cell count 3.5×10⁹/l, neutrophils 1.9×10⁹/l, platelet count 90×10⁹/l, concentrations of sodium 129 mmol/l, potassium 2.7 mmol/l, calcium 1.86 mmol/l, creatinine 48 μmol/l, urea 7.1 mmol/l, albumin 22 g/l, fibrinogen 46 g/l and fibrin degradation products >20 μg/ml, prothrombin time 51 seconds (control 14 seconds), partial thromboplastin time 35 seconds (control 32 seconds), aspartate aminotransferase 152 U/l and creatine phosphokinase 221 U/l. GABHS was grown from blood, fluid from bullae, and her nose. Penicillin was added to her antimicrobial therapy.

After resuscitation her condition improved but she continued to be febrile and developed swelling over her left forearm and calf. She was referred to the Hospital for Sick Children with a possible diagnosis of necrotising fasciitis. On arrival she was febrile (39°C) with a heart rate of 190 beats/min. She had enlarged and tender lymph nodes in the left cervical chain and generalised subcutaneous oedema. A left sided cervical mass anterior to the carotid vessels was demonstrated on cervical ultrasounds and thoracic computed tomography. A technetium white cell scan suggested an inflammatory lymphadenitis as there was marked focal uptake of the labelled white cells. A nuclear magnetic resonance scan revealed multifocal soft tissue lesions in the left side of the neck and extending into the superior mediastinum. Surgical exploration was carried out, and necrotic tissue was obtained, but there was no evidence of pus formation. Histologically, necrotic and infarcted tissue was seen which contained Gram positive cocci in chains. No growth in culture was observed. Gentamicin was discontinued and rifampicin commenced.
Extensive desquamation became apparent by day 8 after admission. After surgery, the child started to improve and the fever abated although she developed severe hypokalaemia (potassium concentration 14 mmol/l) which responded to treatment. She was discharged two weeks later. Extensive virological and bacteriological tests failed to show any other pathogen. There was progressive clinical and radiological resolution of the cervical mass over the next six weeks.

Immunological investigations showed normal total immunoglobulins, Nitroblue tetrizolium reduction and lymphocyte responses and subsets, but low IgG1 and IgG2 values were demonstrated on initial investigation. On repeat studies four months later all immune function tests were normal.

Case 3
A 13 day old girl was referred to the surgical unit at the Hospital for Sick Children, London, with a three day history of erythematous rash and diarrhoea, vomiting for 24 hours, and refusal to feed. On admission, examination showed she had a toxic appearance, central cyanosis, and poor peripheral perfusion. Her blood pressure was 54/30 mm Hg, heart rate 160 beats/min, and central temperature 39.2°C with a gap between central and peripheral temperature of 3.6°C. Her abdomen was grossly distended and rigid, and the bowel sounds were absent. The rash had become confluent and spread to her back. Initial investigations recorded haemoglobin concentration 108 g/l, white cell count 23.5 x 10⁵/l with 93% neutrophils, platelets 92 x 10⁹/l, concentrations of sodium 125 mmol/l, potassium 3.3 mmol/l, creatinine 53 mmol/l, urea 9.3 mmol/l, calcium 2.1 mmol/l, and albumin 24 g/l, prothrombin time 39 seconds (control 10–14 seconds) and partial thromboplastin time more than 120 seconds. Abdominal radiographs showed considerable bowel distension and evidence of free fluid.

Over the next 18 hours she became profoundly shocked and required over 300 ml/kg of plasma and crystalloids in the first 18 hours to maintain perfusion, blood pressure, and urine output. A laparotomy was performed because a surgical cause of the shock and the abdominal findings could not be excluded. Purulent peritoneal fluid was found but no other pathology. Microscopic examination contained 4500 white blood cells/l, protein 10 g/l, and abundant Gram positive cocci. High dose penicillin was administered. Blood and peritoneal cultures grew GABHS sensitive to penicillin.

After the operation she required mechanical ventilation for three days. Two days later she began to desquamate and this continued for more than one week, affecting most of her body. Over the next 10 days she continued to have a spiking fever (39–39.5°C), associated with leucocytosis and neutrophilia. Chest radiographs showed patchy consolidation in the right lower lobe. Subsequently, her clinical condition improved, and her renal function, electrolyte values, and platelet count slowly returned to normal. The patient was finally discharged after 22 days in hospital having discontinued antibiotic therapy the day before. She continued having intermittent fevers for a further 20 days. On follow up one and four months later she was found to be asymptomatic and thriving.

Case 4
Pallor and hypothermia developed in a 10 week old girl. Over the next 18 hours a small red lesion in the left submandibular region became indurated, swollen, and hot, and extended to involve both sides of her neck. On admission to the Hospital for Sick Children she was febrile (39-5°C), her blood pressure was 75/35 mmHg, heart rate 200 beats/min, and respiratory rate 65/min. The oral mucosae were reddened and she was very poorly perfused. She was resuscitated with plasma and crystalloids, requiring 350 ml/kg in the first day. In addition, she was started on flucloxacillin, gentamicin, and ampicillin. Two hours after admission she developed metabolic acidosis, bradycardia, and apnoea, requiring mechanical ventilation. On her initial investigations she was found to have a haemoglobin concentration of 80 g/l, sodium 123 mmol/l, potassium 2.4 mmol/l, chloride 93 mmol/l, calcium 1.9 mmol/l, high of creatine phosphokinase at 826 U/l, and prolonged coagulation tests. Two right sided focal seizures were observed in the first 6 hours. Cerebrospinal fluid examination was normal. Blood cultures grew GABHS, and penicillin plus gentamicin were continued. Within the first two days, she developed progressive anaemia (lowest haemoglobin 70 g/l) requiring packed red blood cells, and a generalised erythematous rash which later desquamated. Over the next 48 hours, her shock resolved but she continued to require ventilation. Mechanical ventilation was stopped after three days. The cellulitis subsided slowly and the patient was discharged on oral antibiotics on day 14.

Discussion
The four children reported in this series all suffered from a fulminant disorder characterised by shock, multisystem involvement, and a distinctive erythematous rash, which fulfilled the diagnostic criteria for toxic shock syndrome, but was associated not with staphylococcal infection but with GABHS sepsis. These cases are strikingly similar to the reports of streptococcal toxic shock syndrome in adults, and to a similar disorder previously described after varicella infection in three children.

The clinical and laboratory features in these cases are sufficiently distinctive and dramatic that they could hardly have gone unrecognised by clinicians in the past few decades. The question therefore arises as to whether the growing number of reports of streptococcal toxic shock syndrome represents the emergence of a 'new' streptococcus associated syndrome, or whether it reflects the rediscovery of an entity which may have been more common in the preantibiotic era.

Before 1940, streptococcal infections accounted for a major proportion of infectious
conditions seen in many centres in developed countries. Deaths from streptococcal bacteraemia, severe scarlet fever, and erysipelas were common. The fatality rate for streptococcal bacteraemia was found to be 72% in the total population and 62% in children under 15 years old in 1937. Based on the clinical description of the disease in these patients, it is possible that the disorder now termed streptococcal toxic shock syndrome accounted for some of the severe cases and deaths. With the decline in the incidence of streptococcal infections in the developed world, modern clinicians may have simply lost their familiarity with this particular complication. However, a definite increase in the incidence of serious disease associated with GABHS has been noted in the past decade. Reports describing severe generalised and focal infections in children with and without underlying disorders have appeared. In addition, there is evidence that non-suppurative complications of streptococcal infection, such as rheumatic fever, have re-emerged in scattered areas in the United States.

The pathogenic mechanisms by which the streptococcal toxic shock syndrome is caused are unknown, but it is likely that the production of one or more toxins induces the clinical manifestations of the disease. GABHS has the capability to produce at least four serologically different types of exotoxins. All of them are pyrogenic, may enhance host susceptibility to lethal endotoxemic shock, produce non-specific stimulation of T lymphocyte proliferation, enhance delayed hypersensitivity, and suppress immunoglobulin synthesis. In addition, they may act as potent release inducers of tumour necrosis factor. In view of the clinical similarities of the staphylococcal toxic shock syndrome to the syndrome seen in our patients, it is of interest that there seems to be considerable amino acid homology between A and C streptococcal toxins and staphylococcal enterotoxins. These toxins not only have a similar structure but also common modes of action on the immune system. TSST-1 and other staphylococcal enterotoxins, streptococcal pyrogenic exotoxins, and some mycoplasma toxins act as superantigens, binding to specific variable β chain regions of the T cell receptor in association with human class II major histocompatibility complex proteins, and stimulating T cell proliferation and cytokine release by the T cells. Release of these inflammatory mediators probably accounts for the clinical manifestations of both the staphylococcal and streptococcal associated diseases.

Despite the clinical similarities and the common mode of action of their related toxins, there are a number of clinical differences between the streptococcal and the staphylococcal syndromes. In staphylococcal toxic shock the site of staphylococcal infection is often a trivial focus or asymptomatic colonisation, and bacteraemia seldom occurs. In contrast, most cases of streptococcal toxic shock syndrome are associated with severe streptococcal focal infection and bacteraemia. Desquamation is less frequently seen in the streptococcal syndrome. Among 26 adults only eight (31%) had desquamation. In view of the extensive soft tissue involvement in streptococcal toxic shock, surgical intervention is more commonly required than in the staphylococcal syndrome. Finally, the timing of events may differ from that in the staphylococcal syndrome as the rash in the streptococcal syndrome may appear late in the disease and coexist with the desquamation.

From the therapeutic point of view, prompt recognition and understanding of the natural history and progression of the disease should lead to an aggressive intensive care approach. Correction of hypovolaemia by infusion of large amounts of colloid, inotropic support, and if necessary ventilatory assistance must be implemented to correct shock and restore adequate oxygen delivery to the tissues. In addition, prompt antimicrobial therapy should be started, and penicillin remains the drug of choice for GABHS infections. Until the microbial cause has been identified, antistaphylococcal cover should be included. Surgical intervention to remove focal infection and reduce the amount of toxin released may be necessary. Despite the fulminant nature of the illness and the prolonged and complicated course, complete recovery is possible with early and aggressive treatment.

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