Toxic shock syndrome

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SUMMARY Presenting features and clinical manifestations of six patients with toxic shock syndrome are reported. In four of the six cutaneous injury, sometimes trivial, occurred before the onset of symptoms and may have been a causal factor. All six children recovered. The need for early recognition and intensive management in this life threatening condition is discussed.

Toxic shock syndrome is an acute febrile illness with mucocutaneous manifestations and multisystem involvement, often associated with focal staphylococcal infection. Although Todd originally described the disorder in children,¹ with a subsequent report of childhood toxic shock syndrome,² publicity given to the disorder in relation to menstruation and tampon use has resulted in its being considered a disease of menstruating females, with little relevance to paediatric practice.³ Although several thousand cases of the tampon associated disease have been reported in the United States, it seems to be uncommon in the United Kingdom, and there have been no previous reports here of its occurrence in children.⁴ While most cases continue to be associated with menstruation and tampon use, there are increasing reports of cases associated with extravaginal infection.⁵ We report six children with toxic shock syndrome.

Patients and methods

Six children, aged 11 months to 10 years, in whom a clinical diagnosis of toxic shock syndrome was made on the basis of the criteria specified by the Centres for Disease Control, Atlanta (Table 1),⁶ presented between November 1981 and December 1983. Five of the patients were admitted to The Hospital for Sick Children, Great Ormond Street and one to Hillingdon Hospital. Microbiological, haematological, and biochemical investigations were performed in the laboratories of the respective hospitals. Staphylococcal isolates (where obtained) were sent to Dr M De Saxe, Public Health Laboratories, Colindale for phage grouping and toxin identification. Staphylococcal antinuclease and anti-

Table 1 Case definition of toxic shock syndrome*

Temperature > 38.9°C
Rash: diffuse macular erythroderma
Desquamation particularly of palms and soles 1-2 weeks after onset of illness
Shock with hypotension and poor peripheral perfusion
Multisystem involvement—3 or more of following:
Vomiting or diarrhoea at onset of illness
Severe myalgia or raised creatine phosphokinase†
Conjunctival hyperaemia or oropharyngeal hyperaemia
Renal: elevated blood urea or creatinine† or pyuria without urinary infection
Hepatic: raised alanine or aspartate transaminases†
Central nervous system: alteration of consciousness
Haematologic: <100 × 10 ⁹ /l platelets
Negative results on:
Blood, throat or cerebrospinal fluid cultures (except <i>Staphylococcus aureus</i> positive blood cultures).
No rise in titre to Rocky Mountain spotted fever, leptospirosis, or rubeola.

*Denotes case criteria after Reingold *et al.*⁶

†Values twice upper limit of normal for laboratory.

staphylolysin assays were also performed at the Public Health Laboratories.

Case report. A previously well 18 month old Pakistani girl (case 1) was admitted to a local hospital with a two week history of intermittent fever and watery diarrhoea that had worsened in the

three days before admission. Her condition continued to deteriorate subsequently. Fever and watery diarrhoea persisted and she became shocked, confused, and oliguric. Despite treatment with large volumes of intravenous colloid, diuretics, and antibiotics she became anuric and was transferred to The Hospital for Sick Children.

On admission she was severely shocked with hypotension (systolic blood pressure 40 mm Hg) and had an appreciable gap between central (40°C) and peripheral temperature (26°C). She was comatose, and responded only to painful stimuli. There was a generalised macular erythroderma, sparing the palms, and peripheral oedema. Her lips were cracked with oropharyngeal and conjunctival hyperaemia. She had a noticeable tachycardia, with a gallop rhythm, and respirations were laboured. Her abdomen was distended and her liver enlarged.

Results of initial investigations were: haemoglobin 7.9 g/dl with crenated red cells; white cell count $25 \times 10^9/l$, with a neutrophil leucocytosis and left shift; platelet count $43 \times 10^9/l$; urea 28 mmol/l; creatinine 200 $\mu\text{mol/l}$; sodium 127 mmol/l; arterial pH 7.0; Po_2 7 kPa; Pco_2 8 kPa; base deficit 14 mmol/l; prothrombin time 68 seconds (control 14 seconds); partial thromboplastin time 120 seconds (control 40 seconds), fibrin degradation products 10 to 40 $\mu\text{g/ml}$ (normal <10); alanine transaminase 450 U/l; aspartate transaminase 1474 U/l; bilirubin 31 $\mu\text{mol/l}$; and albumin 28 g/l. Chest radiograph showed bilateral diffuse lung opacities suggesting pulmonary oedema or shock lung, and abdominal radiograph showed distended small and large bowel.

In response to her respiratory failure, shock, and coma she was electively intubated and ventilated. High pressures and high concentrations of oxygen were required to achieve adequate oxygenation. Dexamethasone was used to control cerebral oedema. Shock was treated initially with volume replacement, 300 ml per kg of colloid being infused during the first 48 hours to restore the central venous pressure. Because of persistent poor perfusion and reduced cardiac output, inotropic support with dopamine and vasodilation with hydralazine were started. Peritoneal dialysis was begun, initially

using a bicarbonate dialysate to correct the acidosis. Anaemia and disseminated intravascular coagulation were corrected with infusions of blood and fresh frozen plasma. Penicillin, chloramphenicol, cloxacillin, and metronidazole were administered while awaiting bacterial culture results. In response to treatment, her shock resolved and her blood pressure, neurological condition, and renal function returned to normal. Skin desquamation began on the eighth day and continued for two weeks. She subsequently made a complete recovery.

Bacterial and viral cultures from all sites were negative except for *Staphylococcus aureus* (resistant to penicillin) isolated from nose, throat, sputum, and a central venous catheter tip. The serum staphylococcal antinuclease on the 18th day after hospital admission was 16 U/ml (normal <4) and anti-staphylolysin 2 U/ml (normal <2). The phage group of the staphylococcus was 3 (type 6, 47, 54, 81) and it produced staphylococcal enterotoxin B. Serological tests for a wide range of organisms including leptospirosis, streptococcus, and rickettsiae were negative.

Clinical and laboratory findings

This patient is representative of all six. Their clinical details are shown in Table 2 and the results of laboratory investigations in Table 3. All presented with fever and diarrhoea and developed a characteristic macular erythroderma, not unlike a scarlatiniform rash, sometimes occurring initially over the trunk but inevitably spreading to the arms and legs. The rash was often more noticeable in the flexural areas, and was occasionally associated with purpura. Generalised desquamation, including the palms and soles, invariably occurred within two weeks of onset of the illness. Of particular interest in five of the six patients was the history of a cutaneous insult (either an abrasion or scald) or recent surgery that may have acted as a site of entry for the staphylococcus. Mucous membrane changes, oropharyngeal oedema, ulceration, and conjunctivitis, usually developed soon after the onset of fever. All patients were confused and restless and these states were associated

Table 2 Initial features in six patients with toxic shock syndrome

Case no	Age (yrs)	Sex	Initial event	Prodromal features	No days after initial event
1	1.5	F	Nil	2 weeks fever, vomiting, diarrhoea, rash	—
2	2	M	Left knee abrasion	Fever, vomiting, diarrhoea, convulsion	4
3	4	M	Right femoral osteotomy for Perthe's disease	Fever, vomiting, diarrhoea	2
4	1.1	M	Hot water scald to face and trunk	Fever, diarrhoea, rash, convulsion	2
5	0.9	M	Hot water scald to left leg	Fever, convulsion	2
6	9	M	Abrasion to left arm and shoulder	Fever, diarrhoea, rash	1

Table 3 Focus of infection and site of *Staphylococcus aureus* isolation

Case no	Focus	Source	Phage group	Toxin
1*	Unknown	Nose, throat, sputum, CVP line tip	3 (type 6,47,54,81)	Enterotoxin B
2	Left knee abrasion	Blood	1 (type 29,52,80,81)	Enterotoxin F
3	Osteotomy wound	Blood, nose, throat, wound	1 (type 29,52,80,77)	Exotoxin C, enterotoxin F
4*	Facial, trunkal scalds	Scald	Untypeable <i>Staphylococcus aureus</i>	
5*	Left leg scald	No isolate		
6*	Left shoulder abrasion	No isolate		

*Cultures taken from these patients after beginning antibiotics.

Table 4 Laboratory investigations in six patients with toxic shock syndrome at the height of illness

Investigations	Patients (range)	Mean (n)	Reference ranges
Blood			
Haemoglobin (g/dl)	7.9–12.7	9.8 (6)	11–17
White cell count ($10^9/l$)	7.4–25	13.7 (6)	6–15
Neutrophils (%)	57–89 (all toxic granulation and left shift)	75 (6)	25–62
Platelets ($10^9/l$)	16–85	45 (6)	150–400
Blood coagulation			
Prothrombin time (sec)	15–68	28 (6)	13–14
Partial thromboplastin time (sec)	36–122	59 (6)	37–40
Thrombin time (sec)	7.5–13.5	10.8 (6)	8–11
Fibrin degradation products ($\mu g/ml$)	<10–160	—	2.1–7.7
Acid base status of arterial blood			
pH	7.0–7.48	7.31 (6)	7.38–7.42
Pco ₂ (kPa)	2.48–8	4.06 (6)	4.7–6.0
Po ₂ (kPa)	5.6–17	10.1 (5)	11.3–14
Standard bicarbonate (mmol/l)	9.9–17	14.4 (6)	21–25
Base deficit (mmol/l)	5–15	10 (6)	–2–+2
Plasma			
Sodium (mmol/l)	121–135	129 (6)	135–143
Potassium (mmol/l)	2.34–3.87	3.12 (6)	4.10–5.60
Urea (mmol/l)	6.9–40.6	21.5 (6)	2.5–7.5
Creatinine ($\mu mol/l$)	62–421	165 (5)	28–61
Total calcium (mmol/l)	1.18–1.87	1.52 (5)	2.13–2.62
Albumin (g/l)	26–37	29 (6)	35–55
Globulin (g/l)	20–28	26 (6)	18–36
Bilirubin ($\mu mol/l$)	<12–31	—	<17
Aspartate transaminase (U/l)	90–1496	373 (6)	20–50
Alanine transaminase (U/l)	42–421	178 (5)	10–35
Creatine phosphokinase (U/l)	537–3300	2112 (3)	20–130
Glucose (mmol/l)	3.7–11.6	6.15 (4)	3.5–5.0

with convulsions early on in the courses of illness in three. Coma and raised intracranial pressure occurred in cases 1 and 5. All patients were shocked, with hypotension and poor peripheral perfusion, and all had a wide gap between the central (rectal) and peripheral (skin) temperatures.

Laboratory investigations confirmed multisystem involvement with renal impairment, and raised transaminases and creatine phosphokinase concentrations in those patients tested. Anaemia, thrombocytopenia, and leucocytosis were invariably present with prolonged clotting and raised concentrations of fibrin degradation products

suggesting disseminated intravascular coagulation (Table 4).

Management

Shock was the major problem in all patients. Very large volumes of plasma, blood, and crystalloids were required to restore circulating volume. In some, during initial resuscitation, up to 300 ml/kg were required over the first two days. These large volumes could only be given with careful monitoring of central venous pressure, arterial pressure, and central and peripheral temperatures. Where poor

perfusion persisted despite volume replacement, inotropic support and vasodilators were infused.

Ventilation was required for respiratory failure and management of coma in cases 1 and 5. Cerebral oedema was treated with hyperventilation, mannitol, and dexamethasone, and with regulation of fluid replacement. Intracranial pressure monitoring was undertaken in case 5. Although the impaired renal function was mainly pre-renal in origin, and responded in most cases to volume replacement, diuretics, and inotropic support, peritoneal dialysis was required in cases 1 and 4.

Disseminated intravascular coagulation and anaemia were treated with infusions of fresh frozen plasma and blood. Antibiotics were given while awaiting results of cultures. In the first patients, broad spectrum antibiotics were used, but once the features of the syndrome were identified, specific treatment with anti-staphylococcal antibiotics resistant to penicillinase was instituted. Cases 2 and 5 received intravenous hydrocortisone early on in the course of their illnesses because of presumed septicaemic shock.

All six patients recovered completely.

Discussion

Toxic shock syndrome is an acute febrile illness, the major manifestations of which are high fever; diffuse erythroderma followed by desquamation, oropharyngeal, conjunctival, or vaginal hyperaemia; hypotension; and multisystem dysfunction which must include at least three of the following: vomiting or diarrhoea, alteration of consciousness, impaired renal function, impaired hepatic function, thrombocytopenia, raised muscle creatine kinase, and cardiopulmonary dysfunction (Table 1).⁶

Although not a prerequisite for diagnosis, the syndrome is associated with focal infection or colonisation with *Staphylococcus aureus* in a high proportion of cases. The original case definition excluded cases with a staphylococcal bacteraemia. The constellation of symptoms, however, is sufficiently distinctive to warrant the inclusion of such cases, and accordingly the diagnostic criteria have recently been altered.⁷ Our six patients fulfil the diagnostic criteria and are the first cases reported in children in the UK. They illustrate many of the problems of diagnosis and management of the syndrome.

Toxic shock syndrome has features in common with several other diseases such as leptospirosis, streptococcal scarlet fever, Rocky Mountain spotted fever, staphylococcal scalded-skin syndrome, atypical measles, Kawasaki disease, and the Stevens-Johnson syndrome. Toxic shock syndrome can,

however, be distinguished as a distinct clinical entity from all of these illnesses. The infectious illnesses such as leptospirosis and streptococcal infections are excluded by appropriate cultures and serological tests. Kawasaki disease, with which the fever and mucocutaneous manifestations of toxic shock syndrome show considerable similarities, is not associated with shock unless myocardial infarction has occurred, and thrombocytosis rather than thrombocytopenia is invariably present. Furthermore Kawasaki disease is not associated with staphylococcal infection; Stevens-Johnson syndrome usually follows drug exposure and is likewise not associated with staphylococcal infection. The scalded skin syndrome (toxic epidermal necrolysis) is associated with staphylococcal infection but shock and multi-system involvement are not typical, and the skin lesions are histologically distinct from those found in toxic shock syndrome.¹

In their original description of toxic shock syndrome, Todd *et al* noted that severe multisystem involvement occurred at sites distant from the focus of staphylococcal isolation, which was often a trivial infection or asymptomatic colonisation. In support of the idea that the illness was toxin mediated rather than due to direct bacterial invasion, they isolated an epidermal toxin (distinct from the epidermolytic toxin associated with the scalded skin syndrome).¹ Many other studies have since confirmed the association of toxic shock syndrome with focal staphylococcal infection.³⁻⁶ The staphylococcal strains associated with the syndrome show considerable phenotypic differences from those isolated from patients with other staphylococcal infections.^{8,9} They tend to react with group 1 bacteriophages, produce less haemolysin, are heavy metal resistant, bacteriocin susceptible, and show increased proteolytic activity. A variety of extracellular toxins are associated with toxic shock syndrome strains, and these are found infrequently in strains linked with other disorders. In addition to Todd's original epidermal toxin, a pyrogenic exotoxin C,¹⁰ enterotoxin F,¹¹ and toxic shock syndrome marker protein⁸ have all been identified. The diversity of products produced by toxic shock syndrome strains has made it difficult to assign them individual pathogenic importance, and it is likely that these proteins are markers of the potential to cause the disorder, rather than being directly pathogenic.⁸ More recently, it has been suggested that the proteins and strain characteristics linked with toxic shock syndrome may be coded for on phage or plasmid genetic material incorporated into the staphylococcal DNA. Alternatively these properties may result from post translational modification of staphylococcal products mediated by protease

activity arising from a single genetic transformation.⁹ Furthermore the failure to identify a specific pathogenic toxin suggests that the disorder may be mediated by activation or release of host inflammatory mediators, such as complement, kinins or the prostaglandins.

Although similar illnesses had been reported before its formal description,¹² toxic shock syndrome does seem to be increasing in prevalence, first in the USA and possibly now in Britain.⁴ Since 1981 the number of cases linked with tampons has declined, possibly due to a change in tampon usage, but the proportion of cases not associated with menstruation continues to rise.¹³ Whether this apparent increase in incidence is due to increased recognition, or spread of a new strain of staphylococcus capable of producing toxic shock syndrome is not yet clear.

The treatment of toxic shock syndrome requires prompt and aggressive management of the shock and resulting multisystem failure. Severe intravascular volume depletion due to massive capillary leakage may coexist with impaired myocardial function. Intensive monitoring is therefore essential to guide volume replacement and cardiovascular support with inotropic and vasodilator drugs. Ventilation, dialysis, intravenous nutrition, and measures to reduce cerebral oedema are often necessary. Antistaphylococcal antibiotics resistant to penicillinase should be given to eradicate the infection, and there is recent evidence that steroids (such as methyl prednisolone) diminish the toxicity of strains of staphylococcus associated with toxic shock syndrome, resulting in more rapid clinical improvement.^{8, 14} With these measures, even severely affected patients may recover.

Finally, the occurrence of six cases of toxic shock syndrome in two closely related centres within a two year period suggests that the disease may be becoming more common in this country. In none of our patients was this diagnosis considered before referral, despite the presence of typical diagnostic features. Paediatricians should therefore be alerted

to the occurrence of toxic shock syndrome in this country.

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