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(Accepted 11 July 1996)

Lesson of the Week

Potentially lethal bacterial infection associated with varicella zoster virus

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Occult bacterial infection with group A streptococcus or *Staphylococcus aureus* may complicate chickenpox and cause potentially lethal disease

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BMJ 1996;313:283–5

Chickenpox is generally considered to be a benign self limiting illness in children. Indeed, mild secondary bacterial infection of the skin, of little clinical importance, is the most common complication of varicella virus infection.[1 2] There has been a recent increase in reports of serious bacterial infections, however, both during or after chickenpox.

We reviewed the case notes of 13 children (mean age 30 months; seven boys, six girls) who presented to our unit over 12 months (1994-5) with bacterial sepsis associated with chickenpox. We also included one case (case 1) who died of group A streptococcal septicaemia at another hospital.

Case report

An 11 month old girl was admitted with fever, poor feeding, and diarrhoea on the fourth day after the onset of chickenpox. She had a fever of 40°C and a haemorrhagic pustular rash. There was periorbital oedema and conjunctival injection with oral erythema and a 1 cm diameter black necrotic lesion around a vesicle on the dorsum of her left hand. There was no neurological or cardiovascular compromise at presentation.

Twenty four hours later she became shocked with a capillary refill time of four seconds, peripheral core temperature difference of 8°C, blood pressure of 75/40 mm Hg, and a pulse of 150 beats/min. She developed increasing oedema and required supplementary oxygen. Despite resuscitation with colloid and a course of antibiotics she continued to deteriorate and was intubated and mechanically ventilated. Inotropic support and large volumes of colloid were required to correct the shock.

Initial laboratory investigations indicated a haemoglobin concentration of 103 g/l, a white cell count of 7.2 $\times 10^9$/l, and a platelet count of 119 $\times 10^9$/l with normal clotting. There was hyponatraemia with a plasma sodium of 126 mmol/l. She was treated with intravenous acyclovir, flucloxacillin, and gentamicin. An echocardiogram and a computed tomogram of the brain showed normal functioning.

Incision and drainage of the necrotic hand lesion was performed, with a rapid improvement in her clinical condition; pus from this lesion grew *Staphylococcus aureus*. Staphylococcal enterotoxins A, C, and D were isolated from this sample.

Results

Features of all 13 cases are summarised in table 1. The mean time to presentation from onset of the chickenpox rash was five days, range two to 14 days. *S aureus* was isolated from blood cultures in three children and from other sites, including infected skin, nose, and throat, in five children. Group A streptococcus grew in blood cultures from two children and from skin lesions or lymph node in two others. Two children had Gram negative septicaemia, one with *Escherichia coli* and another with *Pseudomonas* sp. Six of the children presented with features of toxic shock syndrome. Nine of the 12 children presented with a temperature higher than 39°C. Only three children had a substantially raised white cell count and only five had neutrophil leucocytosis. In four of the children we also measured toxin production from the bacterial isolate. In all four cases either staphylococcal or streptococcal enterotoxins were detected.

Discussion

Complications of varicella zoster virus infection are diverse and well recognised and include Reye's syndrome, cerebellar ataxia, arthritis, thrombocytopenia, and purpura fulminans[1] associated with low protein

Table 1—Clinical and laboratory features of 13 patients with invasive bacterial infection (group A streptococcus or Staphylococcus aureus) following on from chickenpox

Case No	Age (months)	Sex	Days since onset of rash	Organism isolated from blood (or other site)	Clinical features	Temperature at presentation (°C)	Initial white cell count (× 10^9/l)	Initial neutrophil count (× 10^9/l)	C reactive protein (mg/l)	Toxin detected
1	24	M	3	Group A streptococcus	Convulsions, shock; died	39.6	11.1	9.1		
2	11	F	4	*S aureus (skin)*	Shock, haemorrhagic rash	40.0	7.2	3		SEA, SEC, SED
3	23	M	2	*S aureus*	Toxic shock syndrome, infected skin lesions	39.1	28.8	14.9	154	
4	84	F	6	*Pseudomonas*	Status epilepticus		5	3.2	28	
5	1.5	M	2	*S aureus*	Shock	39.0	6.2	3.8	9	
6	4	M	2	Coliforms	Irritable, unwell looking	39.0	10	2.8	<5	
7	36	F	6	*S aureus* (skin, nose, throat)	Shock, infected skin lesions	39.0	19.6	13.4		SEA, SEB
8	20	F	14	Group A streptococcus (lymph node)	Lymphadenitis	39.2	19	12	110	
9	17	M	10	No organism	Shock	37.9	5.9	2.3	<5	
10	48	M	4	Group A streptococcus	Fasciitis	39.0	13.2	11.4	83	SPEA
11	17	F	5	*S aureus* (skin)	Lymphadenitis	38.5	9.8	7.2		
12	60	M	5	*S aureus* (blood and skin); Group A streptococcus (skin, eye)	Toxic shock syndrome, infected skin lesions	36.5	9.4	6.8		
13	48	F	7	*S aureus* (skin)	Shock, infected skin lesions	39.5	12.2	8.2	34	SEC

SEA, SEB, SEC, SED: staphylococcal enterotoxins A,B,C,D; SPEA: streptococcal pyrogenic exotoxin A.

C and S concentrations,[3] but secondary bacterial infection is the most common complication.[4 5]

In a population based study conducted over 20 years in Minnesota, 1 in 1000 children with chickenpox required admission to hospital; the most common complications leading to admission were bacterial superinfection in children under 5 years, varicella encephalitis in 5 to 9 year olds, and varicella pneumonia in adults.[6] Among 2534 patients with varicella seen at one hospital in New York during a five year period, 133 (5.2%) had complications, and of these, 28% had otitis media, 15% bacterial pneumonia, 10% septicaemia, 12% lymphadenitis, 11% cellulitis, 18% abscess, 5% erysipelas, and 3% gangrene.[5] Most bacterial isolates were group A streptococcus or *Staphylococcus aureus*. There are no population based studies of complications of varicella in the United Kingdom.

Fever and irritability are typical early features of both varicella virus infection and bacterial sepsis. In uncomplicated varicella infection, constitutional symptoms are usually resolving by three to four days. Secondary bacterial infection may be likely if the child's fever returns or worsens or if the child deteriorates after an initial improvement. In the first three days of varicella infection, however, early bacterial sepsis can be indistinguishable from uncomplicated varicella zoster virus infection. Four of our 13 cases developed bacterial sepsis within three days of onset of the rash. Laboratory investigations were of little help in distinguishing bacterial from viral infection, as white cell count, neutrophil counts, and C reactive protein concentration were not consistently raised in our cases. Therefore, a high index of suspicion is needed to make the diagnosis of bacterial sepsis in any child presenting with varicella virus infection.

S aureus was isolated from blood cultures in three of our patients who presented with features of toxic shock syndrome. The organism was also isolated from infected skin in five children, four of whom presented with shock. Although not yet included in lists of complications of varicella in standard textbooks,[1 2] staphylococcal toxic shock has been reported in association with chickenpox.[7 8] Other staphylococcal complications of varicella, including staphylococcal scalded skin syndrome,[9] pericarditis,[10] and osteomyelitis,[11] have also been reported. Staphylococcal pneumonia is well recognised as a complication of chickenpox in adults.[12]

Systemic sepsis with group A streptococcus, complicating chickenpox, is increasingly recognised,[4 13-19 20 21] and this organism was isolated from four children in our series. These children may present with streptococcal toxic shock syndrome,[15 22] necrotising fasciitis,[14] osteomyelitis,[23] pyomyositis,[24] gangrene,[25] subgaleal abscess,[26] arthritis,[27] or meningitis[28] associated with varicella. Christie *et al* examined the medical records of 60 children presenting to two centres in the United States with bacteraemia caused by group A streptococcus.[29] Seven (12%) children had varicella infection as the underlying diagnosis. In another study of all 37 children with group A streptococcal disease presenting to Memphis children's hospital during an eight year period, 22% (8) of the children had varicella virus as the underlying infection, and 68% of the isolates produced streptococcal pyrogenic exotoxins (SPE A,B,C).[13]

In our series, group A streptococcus infection was associated with fasciitis and local lymph node disease. A series of 14 children presenting over an 18 month period with group A streptococcal necrotising fasciitis, which was associated with varicella infection, has recently been reported. This study showed the difficulty of diagnosing invasive disease on a background of varicella infection.[14] Pain, erythema, and oedema were universal features of group A streptococcal fasciitis, but pain may also herald the onset of staphylococcal scalded skin, complicating varicella.[30]

In those children presenting with shock, diagnosis is usually readily apparent. Features of toxic shock syndrome include fever, diarrhoea, myalgia, red mucous membranes and lips, strawberry tongue, conjunctival injection, rash, erythema and swelling (and subsequent desquamation) of extremities, tachycardia, hypotension, and neurological dysfunction progressing to coma. Laboratory findings may include a low platelet count, raised transaminase activity, increased plasma urea and creatinine concentrations, electrolyte disturbance, and coagulopathy.[31] Both group A streptococcal disease and staphylococcal infection may present as toxic shock syndrome.[11 12 15 22 32 33] Eight of our patients presented with features of toxic shock syndrome and in three of these children enterotoxin producing strains of *S aureus* were isolated. The staphylococcal enterotoxins and the streptococcal pyrogenic exotoxins belong to a family of toxins which, acting as superantigens,[34-36] stimulate vast numbers of T lymphocytes, causing widespread immune activation, including cytokine production, which may lead to shock.

The reasons for the association of group A streptococcal sepsis with varicella virus infection are not clear. Invasive bacterial infection in varicella zoster virus disease may simply be related to the decreased integrity of the skin as a result of varicella lesions which attenuate the physical barrier to invasion. But this does not explain the late cases of bacterial disease observed up to two weeks after onset of varicella infection,[15] as occurred in one of our cases. An alternative explanation is that varicella infection impairs host immunity. A transient granulocyte killing defect has been reported in one case.[37] The possibility that some viruses might encode proteins (virokines) which interfere with immune responses by blocking cytokines or complement [38 39] is intriguing but has yet to be shown in varicella virus infection.

These cases highlight the seriousness of bacterial superinfection as a complication of chickenpox in children. The possibility of bacterial sepsis, especially caused by group A streptococcus or staphylococcus, should be considered in any child with varicella virus infection who has persistent or recurrent fever after the third day of the illness, or when signs of systemic toxicity appear. Early antibiotic administration and surgical drainage of infective foci may save the lives of patients with septicaemia or toxic shock syndrome. Bacterial sepsis, along with the occurrence of other potentially lethal complications of varicella, adds weight to the arguments for inclusion of varicella virus vaccine into childhood immunisation schedules in the United Kingdom, as is now being considered in the United States.[40]

Funding: None
Conflict of Interest: None

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(Accepted 6 March 1996

ONE HUNDRED YEARS AGO

A STATE DEPARTMENT OF PUBLIC HEALTH.

We are glad to have the assurance that our remarks to the creation of a central department of public health are bearing fruit in different directions. We are glad to know that it is so, since it has long been our opinion that such a department is needed in this country. We have in the last few years seen immense strides in the direction of decentralisation in the way of public health administration, and as a consequence we have now a greatly divided system of local self-government. However many may be the benefits of such a state of things, there are undoubtedly lacking not a few of the good elements which accrue from direct Government supervision of the manner of carrying into effect the multitudinous statutes which have to do with the common weal. Decentralisation has, in fact, gone to such extremes that it needs a strong whip hand, so to speak, to control the numerous small bodies which have been empowered by Parliament in respect of matters pertaining to the national health. All this has brought about an ever-growing feeling amoung sanitarians that some district department should be charged with the direction of the sanitary laws, deeming such a central Board at least as important as that which has to do with the health of beasts. Whether the administration of the Poor Law should be included in the duties of the department is a matter of doubt, though in many respects it is easy to see that the two are intertwined. But apart from that aspect of the case, we would hail with delight a ministry of public health, and, as an accompaniment, a consolidation of the present mass of statutes which have to do with the health of man.

(*BMJ* 1896;ii;1466.)