Prognostic factors in acute meningococcaemia

L. S. LEWIS

Department of Paediatrics, Ahmadu Bello University Hospital, Zaria, Nigeria

SUMMARY During a meningococcal (group A) epidemic, 47 Nigerian children with acute meningococcaemia without meningitis were studied. Their mortality rate was 43% compared with 8% during the whole epidemic. Those presenting with coma and shock had a mortality of 93%, but without shock or coma mortality was only 6%. Coma or shock occurring alone carried an intermediate prognosis. The outcome correlated with initial serum antigen titre, but not with the serum levels of endotoxin, cortisol, or fibrin degradation products. Chloramphenicol was as effective as penicillin. A predictor of expected mortality, based on serum antigen titre and the presence of coma or shock, may allow new forms of treatment to be assessed.

Acute meningococcaemia still has a high mortality during African epidemics (Lapeyssonie, 1963), as in the rest of the world, especially in those patients without meningitis. Mortality rates in such patients were as high as 60% with Flexner’s intrathecal antiserum therapy during the 1930s. Subsequent use of antibiotics, corticosteroids (May, 1960), heparin (Niklasson, et al., 1972), digoxin, and IV fluid regimens (Murray et al., 1974; Cahalane and Waters, 1975) has not lowered the mortality. Edwards (1971) showed that high titres of meningococcal capsular antigen are found in the serum during the fulminant form of the infection, and suggested that a threshold level, beyond which disease is irreversible, might exist. The value of other prognostic indices—such as hypotension, duration of purpura, CSF counts, and peripheral blood counts—has been discussed (Stiehm and Damrosch, 1966; Niklasson et al., 1971). We studied some of these factors and also serum levels of endotoxin and cortisol, and fibrin degradation products (FDP) in an homogenous group of Nigerian children suffering from acute group A meningococcaemia, during a large short-lived outbreak. A report on the general features of the epidemic, with its overall mortality of 8%, is in preparation.

Patients and methods

Patients. 47 children with acute fevers, petechial haemorrhages, and CSFs clear to the naked eye were chosen from a total of 530 paediatric admissions for meningococcal disease. During the 3-month epidemic, this group served to define clinically a syndrome of acute meningococcaemia without meningitis'. Diagnosis was proved in 37 either by the detection of group A antigen by counter-current immunoelectrophoresis (Edwards, 1971), or by a positive culture from blood or CSF. Two of the 10 unproved cases died before they could be investigated. Four others had siblings with proved meningococcal meningitis, and the remaining 4 lived close to known cases.

Age ranged from 1½ to 12 years (mean 5·9) and 26 (55%) were boys. The highest CSF WBC was 250/mm³ (0·250 x 10⁹/l) and 80% of patients had counts lower than 5/mm³ (0·005 x 10⁹/l).

In most patients continuous monitoring of BP, central venous pressures (CVPs), ECGs, and rectal and skin temperatures was maintained.

Treatment. Either benzylpenicillin (1 megaunit 6-hourly IV if patient under 4 years, up to 3 mega-units 6-hourly if over 8 years), or chloramphenicol (25 mg/kg 6-hourly IV) was given.

In any patient with shock (defined as systolic BP <3rd centile for an American population, i.e. <75 mmHg under 4 years, and <85 mmHg over 4 years), IV dextran 70 was given as quickly as possible until CVP and BP were restored.

At first digoxin was given to patients with pulmonary oedema, but later in the epidemic, this treatment was given to all hypotensive patients.

Prednisolone (50 mg 6-hourly IV) was given to some patients late in the epidemic.

Laboratory methods. Studies were performed on encoded specimens of serum and CSF taken at
presentation. Endotoxin assay was used for samples collected in endotoxin-free bottles (after swabbing the skin with iodine) and preserved deep-frozen. With the Limulus test and chloroform-extraction (Levin et al., 1972), the lysate used (Marine Biologicals) could detect a standard endotoxin diluted in serum at a level of 2 ng/ml. A semiquantitative assay of FDP was performed by the slide latex agglutination test (Burroughs-Wellcome). Serum cortisol was assayed by competitive protein-binding (Murphy et al., 1963).

Because of local mores, there were no necropsies.

Statistics. Unproved cases are not included in the results. Nonparametric tests were used if appropriate, and methods are quoted in each case.

Results

Mortality. 20 of the 47 clinically diagnosed cases died. Of the 37 proved cases, 18 (49%) died. All survivors were completely cured. Most (55%) deaths occurred in the first 4 hours in hospital, and 80% during the first 12 hours.

Clinical presentation and prognosis. Of the various presenting features, shock and coma (absence of co-ordinated response to pain) were the most decisive prognostically (Fig. 1). If a child presented with a normal BP and was conscious his chances of recovery were good. Nearly all children presenting with both coma and shock died. Shock or coma carried an intermediate risk.

Length of history did not correlate with mortality: 80% had been ill for <24 hours, and 40% for <12 hours. The proportion dying in each group was the same.

All 47 children had conjunctival petechiae easily seen, and 20 had purpura less obvious on their dark skin. Those with skin purpura had a higher mortality than those without (50% compared with 37%), but this was not statistically significant.

The height of fever did not relate to mortality, but a rectal temperature exceeding skin temperature by 3°C or more (reflecting the vasoconstricting shock) did.

Clinical progress. Some patients, although initially well, deteriorated during the first 8 hours of observation, while others made a progressive recovery (this difference was shown to relate to serum antigen titre). The mode of deterioration was characteristic; rate and depth of respiration increased, conscious level fell, and purpura extended as CVP fell to zero. Heart rate rose to over 150/min as BP fell, often suddenly and to unrecordably low levels. Although BP and CVP rose with dextran, the coma and hyperventilation usually persisted, with tetany and features strongly suggesting pulmonary oedema (widespread rales and copious frothy blood-tinged sputum). The CVP, usually held below 10 cm, never exceeded 14 cm, while ECG showed sinus tachycardia (150–180/min), S–T segment changes (usually digitalis effect), and an unchanging normal axis. Arrhythmia was rare: in one patient a few ventricular ectopics were seen and, in one other, a wandering pacemaker. Bleeding from mucosae or venepuncture sites occurred in only the comatose and deeply shocked patients, all of whom had received dextran.

Treatment. Penicillin and chloramphenicol were equally effective. In patients in whom the diagnosis was proved, 7 out of 14 given chloramphenicol and 11 out of 22 given penicillin died. The two groups were evenly matched for age, presenting features, and serum antigen titre.

Dextran 70 was almost always effective in restoring CVP and BP; usually 20 ml/kg was required. In the absence of controls, a reduction in mortality cannot be shown.

Digoxin had no discernible effect clinically, but ECG showed S–T effect without obvious toxicity.

Prednisolone, given to only 6 patients, had no apparent effect. Phenoxybenzamine was given to 2 patients in unresponsive shock. One died after an hour: in the other, despite rapid resolution of shock and pulmonary oedema, coma persisted until death 4 weeks later.

Laboratory findings.

Serum antigen

The presence of group A antigen in serum correlated with mortality; 17 (57%) out of 30 antigen-positive cases died while none of the 6 antigen-negative (but proved) cases died (P<0.025 Fisher's exact test). The titre of antigen also correlated with mortality (Fig. 2; P<0.001 Mann-Whitney test).
had positive results. There was no relation between a positive result and either clinical severity or mortality. Death occurred in one out of 6 children with a positive result, and in 2 out of 10 with a negative one.

**Fibrin degradation products**

Initial serum titres showed no correlation with clinical severity, bleeding complications, or mortality. Three out of 7 patients with FDP <10 μg/ml died as did one out of 3 with a level >40 μg/ml.

**Serum cortisol**

Levels are shown in Fig. 4. All are high (normal range 100–500 nmol/l; 3·6–18 μg/100 ml) with no significant difference in mean level between those who lived (708 ±SD 109) and those who died (724 ±SD 273). The levels did not correlate with clinical syndrome, antigen titre, FDP, or endotoxin levels.

**Cerebrospinal fluid**

Antigen was detected in 8 patients' CSF, 4 of whom had cell counts below 5/mm³ (0·005 ×10⁹/l). CSF culture was positive in 10 patients, 3 of whom had cell counts lower than 5/mm³. CSF endotoxin assay was positive in 5 out of 15 patients. None of these findings related to clinical features, serum findings, or mortality.

All patients with an antigen titre <0·25 μg/ml survived, but there was no threshold beyond which death was inevitable. If serum antigen titres are compared with the presenting features (Fig. 3), it is obvious that higher titres relate to more severe disease (P<0·025 Kruskall-Wallis test).

**Endotoxin**

Assays on sera of 7 healthy controls gave one positive result (i.e. >2 ng/ml). Six out of 16 patients' sera had positive results. There was no relation between a positive result and either clinical severity or mortality. Death occurred in one out of 6 children with a positive result, and in 2 out of 10 with a negative one.

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Discussion

The identification of poor-risk meningococcal patients on the clinical findings of petechiae, fever, and clear CSF is imperative during epidemics. Diagnosis may quickly be confirmed by finding group A specific antigen in the blood, and bedside prognostication is improved by antigen titration. Ideas on the mechanism and management of the ensuing catastrophe continually change, so the important facets are considered in the light of our findings.

Banks (1948) described 4 forms of acute meningococcaemia: the ordinary, the 'adrenal', the encephalitic, and the 'mixed' form, corresponding to our clinical categories. His stress on brain injury, supported by necropsy findings, has received too little attention in other studies. This was a crucial prognostic factor in our patients, and was evident as coma regardless of BP, pulmonary oedema without a raised CVP, and tetanic hyperventilation. It was not related to meningitis in the sense of a cell exudate, although in some patients a positive culture or antigen was found in an acellular CSF—a long-known fact (Glasscock, 1935). The shock itself may be of central nervous origin (Ducker and Simmons, 1968), mediated by pulmonary (Udhoji et al., 1963) or splanchnic (May, 1960) pooling, rather than by cardiotoxicity (Levin and Painter, 1966; Hardman and Earle, 1969). Hypotension is preceded by hyperventilation, failing consciousness, and a fall in venous return without actual change in blood volume (May, 1960). The full-blown syndrome with frank pulmonary oedema was seen in several patients at presentation, and therefore cannot be attributed to excessive IV infusion. In our patients digitalisation was of doubtful benefit, but dextran restored BP and CVP. Although 3-blockers and 6-stimulants hold promise for correcting the circulatory changes, in our 2 patients so treated coma persisted until death. There was no evidence that the encephalitis responded to corticosteroids, but its reversal in 6 patients not given corticosteroids was encouraging. 'Supraentral apoplexy' (Waterhouse, 1911) is an unlikely cause of death as shown by the high cortisol levels, clinical findings, and ineffectiveness of corticosteroid treatment.

Endotoxaemia as detected in our patients was also of no prognostic significance; perhaps the Limulus test lacks clinical value (Stumacher et al., 1973), or endotoxin is not the central issue after all (Kass et al., 1973).

Disseminated intravascular coagulation (DIC), although clearly demonstrated in acute meningococcaemia, may likewise be unimportant or perhaps it is unresponsive to heparin. Initial FDP level did not predict progress. Of 70 heparin-treated cases in 15 reports (Niklasson et al., 1972) 38 patients died. A controlled trial of heparin (Manios et al., 1971) did not show significant benefit. The dextran used in our patients may have countered DIC and improved microcirculation, but it was intended primarily as a plasma expander.

High serum antigen levels at presentation, while not invariably fatal, point strongly to a poor prognosis. This free antigen may be a quantitative marker of live organisms, their dead products, or of an ineffective immune neutralisation and/or phagocytosis. In meningococcal meningitis, CSF antigen level has been correlated with brain damage and higher mortality, and serum antigen positivity with higher mortality (Whittle et al., 1976). Further study to define the role of antigen is needed.

Long experience of sulphonamides (May, 1960) and penicillin, and the effectiveness of chloramphenicol in our patients, suggest that the choice between a bactericidal or bacteriostatic drug is immaterial, provided that the organism is sensitive. It seems that fulminant meningococcaemia is caused by unlimited multiplication of unneutralised bacteria which disrupt leucocytes, and activate the complement (Greenwood et al., 1976) and coagulation pathways; perhaps crucially they have direct toxic effects (although possibly not endotoxic) on the brain. Fulminant disease is present in only a small proportion of the population during meningococcal epidemics. The susceptible may have low levels of circulating antimeningococcal antibody (Goldschneider et al., 1969), or a defect of antibody response (Whittle et al., 1976), although polymorph dysfunction cannot be ruled out. Since a few dramatic recoveries have been reported using IV antibacterial (Glasscock, 1935) or antitoxic sera (Hoyne, 1935), and modern treatment persistently fails to reduce mortality, we intend to try the combination of IV penicillin and IV antiserum in severe cases. A simple prognostic index, based on the presenting features of coma, shock, and serum antigen level should help to assess such treatment.

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Addendum

Since submitting this paper, we have found highly significant depressions of serum antithrombin III.
levels correlated with prognosis; this may help to explain the apparent unresponsiveness of the condition to heparin.

References


Correspondence to Dr L. S. Lewis, Ninewells Hospital, Department of Medicine, Dundee DD2 1UB, Angus, Scotland.

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L S Lewis

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