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# *Short reports*

## Endotoxin in meningococcal infections

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SUMMARY 26 children with meningococcal infections were studied to find out the relationship between plasma and cerebrospinal fluid levels of endotoxin, the clinical outcome, the level of antigen in plasma and cerebrospinal fluid, and indices of complement activation and disseminated intravascular coagulation. No association was found between endotoxin levels and the other factors. A high cerebrospinal fluid antigen level in patients with meningitis was associated with a poor prognosis.

In meningococcal infections a positive correlation has been found between the levels of meningococcal polysaccharide antigen in serum and cerebrospinal fluid (CSF), and the clinical course of the disease. CSF antigen levels are generally higher in patients with severe neurological damage than in those without, but for the individual patient the association may not necessarily be close.[1] In patients with meningococcaemia the presence of antigenaemia indicates a poorer prognosis, and the higher the antigen titre the worse the outcome.[2] There is no evidence that the polysaccharide antigen is itself toxic, but a possible explanation for these findings is that the antigen titre in the CSF and serum reflects the presence of other toxic meningococcal products, especially endotoxin. In this study the relationship between the antigen titres, endotoxin levels, serum C3 complement component, and fibrin degradation products (FDP) together with the clinical parameters of coma, hypotension, and outcome were examined in patients with group A meningococcaemia and in patients with group A meningococcal meningitis.

### Patients and methods

26 patients with meningococcal disease were studied at the time of admission to hospital. 16 had acute meningococcaemia and 10 meningitis. A diagnosis of meningococcaemia was made by detecting meningococcal antigen in the serum, or, in a patient with fever, petechiae, and clear CSF, by a positive blood culture. Meningococcal meningitis was diagnosed by detection of meningococcal antigen in the CSF or by a positive CSF culture.

10 patients with meningitis were chosen to include 5 patients who died and 5 who survived without complications, whereas those with meningococcaemia were unselected.

Endotoxin was assayed by the limulus lysate technique, using chloroform extraction to remove the inhibitor from plasma samples and gelation as the end-point. The method of Levin *et al.*[3] was used except that the plasma was rotated in chloroform for 6 hours, and the aqueous layer was diluted in pyrogen-free water to determine the final end-point, which was then compared with a standard *Escherichia coli* endotoxin concentration (Difco). CSF was tested without chloroform extraction. The sensitivity of the method was 0·0625 ng/ml in CSF and 0·125 ng/ml in extracted plasma. Controls included the CSF from 2 patients with febrile convulsions in whom the CSF contained no cells and was antigen-negative and bacteriologically sterile. Inhibitory and sensitivity controls were also included. Meningococcal antigen levels were measured in the serum and CSF by counter-current immunoelectrophoresis.[4] Dilutions of CSF or serum were doubled and then tested against anti-group A meningococcal polysaccharide antiserum (Difco) and the end-point compared with that obtained with a purified group A meningococcal polysaccharide standard. FDP were assayed using a semiquantitative slide latex agglutination test (Burroughs Wellcome). The C3 complement was assayed by radial immunodiffusion; statistical analysis used, where appropriate, Student's *t* test and the Wilcoxon rank sum test, linear regression, and correlation coefficient.

### Results

**Meningococcaemia.** The results of endotoxin, meningococcal antigen, C3, and FDP assays in 16 patients with acute meningococcaemia are shown in Table 1, together with clinical data. The mean

Table 1 *Clinical details, serum antigen, plasma endotoxin, serum C3, and fibrin degradation product levels from 16 patients with acute meningococcaemia*

| *Case* | *Age (years)* | *Hypotension on admission** | *Coma level (0 to 4+)* | *Serum antigen (ng/ml)* | *Plasma endotoxin (ng/ml)* | *C3 (% of normal)* | *FDP (ng/ml)* |
|---|---|---|---|---|---|---|---|
| Survived | | | | | | | |
| 1 | 11 | − | 2+ | 3840 | 0·25 | — | 640 |
| 2 | 9 | − | 2+ | 960 | 0·5 | 120 | 2·5 |
| 3 | 5 | − | 2+ | 120 | 0·5 | 164 | 10 |
| 4 | 8 | − | 1+ | 120 | 0·125 | 124 | 5 |
| 5 | 10 | + | 3+ | <60 | 0·062 | 120 | 20 |
| Mean | 8·6 | | 2 | 1008 | 0·29 | 132 | 135 |
| SD | 2·3 | | 0·7 | 1629 | 0·2 | 21 | 282 |
| Died | | | | | | | |
| 6 | 6 | + | 4+ | 3840 | 0·5 | 86 | 2560 |
| 7 | 12 | + | 2+ | 1920 | 0·125 | 80 | 20 |
| 8 | 3 | + | 4+ | 1920 | 0·5 | 70 | 2560 |
| 9 | 8 | + | 3+ | 960 | 0·5 | 128 | 10 |
| 10 | 3 | − | 4+ | 960 | 0·5 | 80 | — |
| 11 | 3 | − | 4+ | 480 | 0·125 | 76 | 5 |
| 12 | 6 | + | 3+ | 480 | 0·125 | 108 | 40 |
| 13 | 6 | − | 3+ | 240 | 0·125 | 64 | 20 |
| 14 | 9 | − | 3+ | <60 | 0·5 | 90 | 120 |
| 15 | 3 | + | 3+ | <60 | 0·062 | 124 | 5 |
| 16 | 10 | + | 4+ | <60 | 0·062 | 100 | 160 |
| Mean | 6·3 | | 3·4 | 981 | 0·28 | 91 | 550 |
| SD | 3·1 | | 0·7 | 477 | 0·2 | 21 | 1060 |

*Systolic blood pressure <60 mmHg = +.

serum antigen level in those who died was 981 (± 477) ng/ml compared with 1008 (± 1629) ng/ml in those who survived; the mean endotoxin levels were similarly 0·28 (± 0·2) ng/ml and 0·29 (± 0·2) ng/ml. 11 of the 16 patients died, and a poor prognosis was associated with hypotension and coma at the time of admission. No significant difference was found between the endotoxin and antigen levels in those who lived compared with those who died, and correlations between endotoxin, antigen, C3, and FDP levels were not found.

Table 2 *Cerebrospinal fluid endotoxin and antigen concentrations in 10 patients with meningococcal meningitis*

| *Case* | *Endotoxin (ng/ml)* | *Antigen (ng/ml)* |
|---|---|---|
| Survived | | |
| 1 | 0·5 | <60 |
| 2 | 8 | <60 |
| 3 | 2 | 60 |
| 4 | 2 | 60 |
| 5 | 8 | 60 |
| Mean | 4·1 | 36 |
| SD | 3·6 | 33 |
| Died | | |
| 6 | 8 | 1920 |
| 7 | 32 | 960 |
| 8 | 2 | 480 |
| 9 | 2 | 480 |
| 10 | 0·0625 | 240 |
| Mean | 8 | 812 |
| SD | 13·3 | 672 |

**Meningitis.** The levels of antigen and endotoxin present in the CSF of 10 patients with acute meningococcal meningitis are shown in Table 2. The mean endotoxin level in those who died was 8 (± 13·3) ng/ml and in those who survived 4·1 (± 3·6) ng/ml; similarly the results for mean antigen levels were 812 (± 672) ng/ml and 36 (± 33) ng/ml. The mean levels of endotoxin and antigen were higher in those with a fatal outcome, but only the latter attained significance at the 5% level.

## Discussion

Although endotoxin was detected in the CSF or plasma in all our patients, there was no clear association between the amount of endotoxin present and either the clinical course of the illness or the pathophysiological parameters. It is probable that endotoxin does play some part in the development of shock,[5] disseminated intravascular coagulation,[6] and complement activation[7] that are present in patients with meningococcaemia, but if so, it is not a quantitative relationship; perhaps the endotoxin exerts a maximal effect at low levels. In the small number of patients studied, a poor clinical prognosis was associated with high CSF antigen levels in meningitis, confirming the findings of Whittle *et al.*,[1] but a similar relationship was not found in the meningococcaemic patients.

Endotoxin was detected in the plasma of all meningococcaemic patients and in the CSF of all

the patients with meningitis. It is of interest that in 3 of the bacteriologically confirmed cases of meningitis the counter-current immunoelectrophoresis for antigen was negative, yet a positive result to the Limulus test was obtained; this reaffirms the suggestion of Berman *et al.*[8] that the limulus test should be included in the initial assessment of patients who may have early or partially treated Gram-negative meningitis.

The reliability of detecting endotoxin in the CSF of Gram-negative meningitis shown by Berman *et al.*[8] does not, however, obtain in the plasma of meningococcaemic patients, or patients with other Gram-negative bacteraemias.[5]

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# D-lactic acidosis in a boy with short bowel syndrome

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SUMMARY Metabolic acidosis in a 3-year-old child with short bowel syndrome led to the discovery of massive D-lactic aciduria. After normalisation of the intestinal bacterial flora, D-lactate disappeared together with the acidosis. Dysbacteriosis with excessive production of D-lactate by intestinal bacteria (unidentified) and subsequent absorption explains this unusual cause of metabolic acidosis.

L-lactic acidaemia is a well-known cause of acidosis in childhood. D-lactic acid is not normally present in the urine of humans and can easily be overlooked in cases of acidosis.

We report the case of a child with short bowel syndrome in whom acidosis with an increased anion gap led us to the finding of D-lactic aciduria.

## Case report

The patient, a boy born on 8 December 1975, was first seen in the cardiological division of our department at age 3 days because of transposition of the great vessels; a Rashkind septostomy was performed, later followed by a Blalock anastomosis and, at age 20 months, by total correction.

At age 10 months thrombosis of the mesenteric vessels occurred during an attack of gastroenteritis with dehydration. Resection of 140 cm of the small-bowel, the caecum, and 3 cm of ascending colon was necessary. The resulting malabsorption was treated with dietary measures, including medium-chain triglycerides, restriction of disaccharides and, for a period of 9 months, cholestyramine. This treatment was supervised by the local paediatrician and had only partial success: height and weight increases were below normal.

At age 38 months the boy was readmitted to our department because of attacks of 'dyspnoea' and drowsiness. His mother reported that he had had such attacks occasionally since the intestinal resection but that these had increased to an almost daily frequency in the last weeks. On such days he seemed hungry, unhappy, weak, and uncertain in moving; subsequently he started to breathe deeply and became drowsy. This persisted for a few hours and subsided gradually. At no time was he comatose and he did not convulse. Increasing the