PAPERS AND SHORT REPORTS

Meningococcal septicaemia treated with combined plasmapheresis and leucapheresis or with blood exchange

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Abstract

Mortality among patients suffering from meningococcal septicaemia has reached nearly 50% in parts of northern Norway despite intensive care. The activation of complement and blood cells by endotoxin is assumed to be the cause of most of the associated pathophysiological changes. Consequently, it would seem logical to remove such constituents either by combined plasmapheresis and leucapheresis or by blood exchange in patients with a fatal prognosis. Three patients were treated with plasmapheresis and leucapheresis and one with blood exchange. All recovered without sequelae, and no complications or serious problems caused by these procedures were observed.

It is concluded that either combined leucapheresis and plasmapheresis or blood exchange is well tolerated and a valuable supplement to conventional intensive care in fulminant meningococcal septicaemia.

Introduction

Since 1973 there has been an epidemic of group B type 15 meningococcal disease in northern Norway.¹ Both morbidity

and mortality from meningococcal septicaemia have increased considerably compared with before the epidemic.² From July 1979 to December 1982, 25 out of 47 patients admitted to our hospital for meningococcal disease developed fulminant septicaemia; 12 died. None of the patients who on admission fulfilled four or more of the criteria for the disease (see table I) survived despite intensive surveillance and treatment.

Bacterial endotoxin plays an essential part in the pathogenesis of meningococcal septicaemia. Endotoxin may induce complement activation, which causes granulocytes and monocytes to aggregate in vital organs.³⁻⁴ Such sequestered granulocytes have deleterious effects on the cell membrane of endothelial and other cells through their secretion of hydroxy radicals and lysozymes. The activation of monocytes is accompanied by increased synthesis of thromboplastin, resulting in disseminated intravascular coagulation.⁵ Impaired pulmonary, cardiac, renal, and cerebral function due to inadequate peripheral microcirculation may ultimately cause death. Consequently, removal of endotoxin as well as activated cells and plasma components would seem to be a reasonable approach to treatment.

Because of the repeated failure of more conventional intensive treatment, and encouraged by the findings of Schwartzmann *et al*,⁶ we used blood exchange or combined leucapheresis and plasmapheresis to treat four cases of severe meningococcal septicaemia.

Methods

From March to May 1983 three patients with meningococcal septicaemia who weighed over 30 kg were treated with combined plasmapheresis and leucapheresis and one, who weighed less than 30 kg, was treated with blood exchange. Meningococci of serogroup B were cultured from the blood of all four patients. Combined plasmapheresis and leucapheresis was performed with a Hemonetic 30-S blood processor with circulatory access through both femoral veins. During each of the two or three sessions of apheresis 1.6-2.7 l plasma (60% of the estimated volume of plasma) was removed. In addition, about $0.5-1.0 \times 10^{11}$ leucocytes/l and $2.0-4.0 \times 10^{12}$ platelets/l were removed each time. The erythrocytes were reinfused with fresh frozen plasma.

Blood exchange was performed through a femoral artery by repeated

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aspiration with a 20 ml disposable syringe followed by infusion of the same volume of fresh blood. Serum endotoxin was measured by a limulus test using a chromogenic substrate as described by the manufacturer (KabiDiagnostica, Stockholm, Sweden; preliminary method, March 1982). Tissue thromboplastin in plasma was measured as previously described by one of us,⁷ and screening for the complement split product C3d was performed according to the method of Brandslund *et al.*⁸

Conventional treatment included benzylpenicillin 150-200 mg/kg body weight/day (combined with chloramphenicol until the aetiology was verified), methylprednisolone 30 mg/kg (single intravenous dose), and antithrombin III (50 U/kg) if plasma activities were below 80%. Plasma or albumin 5%, or both, were given in the early shock phase. Overhydration was carefully avoided. Frusemide was given regularly to maintain a high urinary output, and ketanserin or sodium nitroprusside to improve the peripheral circulation.

All four patients were given digitalis to prevent myocardial failure. Intermittent positive pressure ventilation with positive end expiratory pressure was started as soon as possible in cases of pulmonary insufficiency. Our routine surveillance programme included invasive monitoring of arterial blood pressure, central venous pressure, and, when possible, pulmonary arterial and wedge pressures.

Case reports

Four patients with meningococcal septicaemia were treated with combined plasmapheresis and leucapheresis or blood exchange; all recovered within 10 days after admission without any sequelae. Table I shows clinical findings and prognostic scores on admission to hospital; table II shows initial values of laboratory variables.

TABLE I—Initial clinical findings and prognostic scores

	Case No			
	1	2	3	4
Duration of illness <12 hours	—	+	—	—
Fever >40°C	—	+	+	+
Impaired peripheral circulation	—	+	+	+
Widespread petechias	+	+	+	+
Lack of neck stiffness	+	+	+	+
Confusion	—	(+)	+	+
Total prognostic scores	2	5.5	5	5

TABLE II—Initial laboratory findings

	Case No			
	1	2	3	4
Leucocytes ($\times 10^9/l$)	21.4	3.2	3.9	8.1
Platelets ($\times 10^9/l$)	162	264	143	50
Endotoxin ($\mu g/l$)	0.58	11.7	6.0	3.1
Monocyte tissue thromboplastin ($\%/10^6$ cells)	0.8	3.2	1.4	1.3
Antithrombin III (%)	72	86	72	119
C3d present	+	+	+	+

Case 1—An 11 year old girl with a 17 hour history of fever, headache, and nausea developed a typical petechial rash shortly before admission. Treatment with intravenous benzylpenicillin (1.2 g), chloramphenicol (1 g), hydrocortisone (100 mg), and dextran 70 (500 ml) had been started before transport to this hospital. On admission the petechial bleeding had progressed to ecchymoses but peripheral circulation and urinary output were satisfactory. Combined plasmapheresis and leucapheresis was performed four and eight hours after admission without any haemodynamic deterioration. The concentration of endotoxin in plasma was reduced from 0.6 to 0.2 $\mu g/l$ during the first session of apheresis and to 0.1 $\mu g/l$ during the second. A similar reduction in the monocyte tissue thromboplastin activity was observed. The following day she showed moderate diffuse intravascular coagulopathy.

Case 2—A 12 year old boy was admitted with a 12 hour history of vomiting, confusion, and temperature reaching 41.6°C. His petechias rapidly increased to disseminated ecchymoses. Benzylpenicillin (1.2 g) and chloramphenicol (1 g) were given intramuscularly one hour before his arrival at hospital. Intermittent positive pressure

ventilation with positive end expiratory pressure was started immediately on admission. Combined plasmapheresis and leucapheresis was performed at four and 10 hours, 1.6 l plasma being removed during each session. There was no urinary output during the first four hours after admission. During the first session of apheresis urinary output increased to 50 ml/hour. Shortly after the start of the procedure we observed a transient drop in blood pressure, which was rapidly reversed by dopamine. A similar circulatory collapse unrelated to apheresis was observed 12 hours later. During the second session of apheresis arterial oxygen pressure increased from 14.8 kPa (111 mm Hg) to 28.5 kPa (214 mm Hg) at a fractional inspired oxygen of 0.8. Plasma endotoxin concentration was reduced from 4.5 to 1.0 $\mu g/l$ and monocyte tissue thromboplastin activity from 4.2%/10⁶ cells to 1.8%/10⁶ cells during the first session of apheresis; a similar reduction was observed during the second session. Over the following three days he had laboratory signs of diffuse intravascular coagulopathy.

Case 3—A 21 year old man developed fatigue, fever, and muscular pain 21 hours before admission. Before being moved to this hospital he was given benzylpenicillin (5 g) and chloramphenicol (1 g) intravenously. On admission he was confused and showed widespread ecchymoses and petechial bleeding. Intermittent positive pressure ventilation with positive end expiratory pressure was started immediately, and combined plasmapheresis and leucapheresis was performed one, seven, and 19 hours after admission to hospital, 2.1, 2.4, and 2.7 l plasma respectively being removed. On admission the endotoxin concentration was 6.0 $\mu g/l$ and the tissue thromboplastin activity in the monocytes 1.4%/10⁶ cells. During the apheresis sessions both these variables fell gradually. Peripheral circulation improved during the first session and an increase in arterial oxygen pressure from 18.4 kPa (138 mm Hg) to 25.0 kPa (188 mm Hg) at a fractional inspired oxygen of 0.5 was observed during the second session. Ketanserin and sodium nitroprusside were not given before or during the first session. He suffered from severe muscular aches for several days.

Case 4—A 3 year old girl had for two months before admission been treated with prednisolone for idiopathic thrombocytopenic purpura. Twelve hours before admission she developed a fever followed by a petechial rash, which initially was mistaken for a relapse of her idiopathic thrombocytopenic purpura. On admission her temperature was 41.2°C. During the next two hours she developed severe hypotension, impaired peripheral circulation, confusion, and convulsions. Artificial ventilation as well as blood exchange were started two and a half hours after admission. A volume of 1.2 l blood was exchanged for fresh donor blood every six hours for the next 36 hours without any circulatory problems. Peripheral circulation improved during the first blood exchange but temporarily decreased thereafter until the next blood exchange. Arterial oxygen pressure increased from 10.5 kPa (79 mm Hg) to 37.9 kPa (284 mm Hg) during the second blood exchange at a fractional inspired oxygen of 0.8 (information was not available on arterial oxygen pressure during the first blood exchange) but thereafter steadily declined to 18.2 kPa (137 mm Hg). After the third blood exchange arterial oxygen pressure reached 27.2 kPa (204 mm Hg) at a fractional inspired oxygen of 0.7. The pupillary light reflexes were not detectable at the time of the first blood exchange but returned to normal during the third. During treatment the plasma endotoxin concentration and monocyte tissue thromboplastin activity gradually decreased from 3.1 $\mu g/l$ and 1.3%/10⁶ cells, respectively, to zero. Interestingly, laboratory signs of disseminated intravascular coagulation were initially not observed in this patient, probably owing to her idiopathic thrombocytopenic purpura.

Discussion

During recent years all patients with meningococcal septicaemia who on admission to our hospital fulfilled at least four of the clinical criteria for the disease have died. Monocyte tissue thromboplastin activities and plasma endotoxin concentrations in these patients regularly exceeded 1.0%/10⁶ cells and 1.0 $\mu g/l$ respectively.⁵⁻⁹ Hence, on the basis of clinical and laboratory criteria, a fatal outcome would have been expected in all but case 1. All four patients recovered, however, without sequelae. During the first session of combined plasmapheresis and leucapheresis and the first blood exchange a clinical improvement in peripheral circulation was observed in all patients; in case 2 urinary output increased. Arterial oxygen pressure

increased during treatment in all except case 1, and in case 4 pupillary light reflexes returned to normal.

The concentration of endotoxin and the activity of monocyte tissue thromboplastin were appreciably reduced during combined plasmapheresis and leucapheresis and during blood exchange treatment. C3d, which was present in the serum of all patients on admission, was not measurable after 24-48 hours of treatment. A similar reduction in endotoxin concentration and monocyte tissue thromboplastin activity during the first 24-48 hours in hospital was also observed, however, in patients with fatal meningococcal septicaemia not treated with apheresis.⁵⁻⁹ C3d was not studied in these conventionally treated patients. This gradual reduction in endotoxin and monocyte tissue thromboplastin activity in patients not treated with apheresis or blood exchange may largely have been due to the binding of circulating endotoxin to cellular membranes with a subsequent reduction in monocyte stimulation. Hence the effect of combined plasmapheresis and leucapheresis cannot be evaluated by any of these laboratory variables.

One or more of the following factors may be responsible for the apparently successful effect of combined plasmapheresis and leucapheresis: (1) removal of plasma containing activated complement, activated clotting factors, and lysozymes secreted from activated granulocytes; (2) removal of activated and aggregated granulocytes, which excrete superoxide and hydroxy radicals and probably impair peripheral circulation³; (3) removal of activated monocytes exposing thromboplastin⁵; (4) removal of activated platelets with endotoxin attached; and (5) substitution of plasma factors by fresh frozen plasma. Concomitant vasodilatation may be less important; one patient (case 3) improved without such treatment.

Technically our study shows that both combined plasmapheresis and leucapheresis and blood exchange may be performed even in critically ill patients with hypotension and poor peripheral circulation. The transient circulatory collapse observed in

case 2 was probably not due to the apheresis as a similar event was observed 12 hours later unrelated to such treatment. In conclusion, it seems justifiable to try combined plasmapheresis and leucapheresis or blood exchange transfusion in critically ill patients with meningococcal septicaemia. The future place of this treatment, however, must be determined by clinical trials. From our limited experience the plasma concentration of endotoxin and the monocyte tissue thromboplastin activity may be of prognostic value.

References

- ¹ Bøvre K, Gedde-Dahl TW. Epidemiological patterns of meningococcal disease in Norway 1975-1979. *NIPH Ann* 1980;**3**:9-22.
- ² Berild D, Gedde-Dahl TW, Abrahamsen T. Meningococcal disease in the Norwegian armed forces 1967-1979. *NIPH Ann* 1980;**3**:23-30.
- ³ Jacob HS. The role of activated complement and granulocytes in shock states and myocardial infarction. *J Lab Clin Med* 1981;**29**:645-90.
- ⁴ Østerud B, Eskeland T. The mandatory role of complement in the endotoxin-induced synthesis of tissue thromboplastin in blood monocytes. *FEBS Lett* 1982;**149**:75-9.
- ⁵ Østerud B, Flaegstad T. Increased tissue thromboplastin activity in monocytes of patients with meningococcal infection related to an unfavourable prognosis. *Thromb Haemost* 1983;**49**:5-7.
- ⁶ Schwartzmann WB, Tillotson JR, Taft EG, Wright E. Plasmapheresis for meningococemia with disseminated intravascular coagulation. *N Engl J Med* 1979;**300**:1277.
- ⁷ Østerud B, Bjørklid E. The production and availability of tissue thromboplastin in cellular populations of whole blood exposed to various concentrations of endotoxin. *Scand J Haematol* 1982;**29**:175-84.
- ⁸ Brandslund I, Siersted HE, Svehaug SE, Teisner B. Double-decker rocket immunoelectrophoresis for direct quantitation of complement C3 split product with C3d specificities in plasma. *J Immunol Methods* 1981;**44**:63-71.
- ⁹ Harthug S, Bjorvatn B, Østerud B. Quantitation of endotoxin in blood from patients with meningococcal disease, using a limulus lysate test in combination with a chromogenic substrate. *Infection* 1983;**11**:192-6.

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Late referral for maintenance dialysis

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Abstract

A study of patients accepted for maintenance dialysis at the Oxford renal unit in 1981 showed that 23 out of 55 patients were referred late, very shortly before the need for dialysis. This pattern of referral was associated with a higher morbidity at the start of dialysis which may have been preventable. In the late referral group 16 patients (70%) suffered major complications and three (13%) died; by contrast, in the early referral group three patients (9%) suffered complications and one died.

Early referral to a renal unit plainly benefits the patient and allows Health Service resources to be used more economically.

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Introduction

In a survey of patients in Britain dying of chronic renal failure the Medical Services Study Group of the Royal College of Physicians identified a group who died shortly after the start of dialysis,¹ and an accompanying leading article suggested that the deaths might have been due to late referral to specialist centres.² We have therefore reviewed the initial hospital morbidity and mortality and the type of dialysis in patients who began treatment for end stage renal failure in Oxford during 1981 classified according to whether they were referred early or late, late referral being defined as within one month before the start of dialysis.

Present study

PATIENTS

In all patients the decision to institute dialysis was based on uraemic symptoms associated with a creatinine clearance of less than 6 ml/min. Fifty five new patients started maintenance dialysis (24.4/million population). Their ages ranged from 17 to 70 years, and the modal age group was 50-59; 16 patients (29%) were over 55. Table I lists their renal diagnoses.

Thirty two patients (58%) referred more than one month before