Heparin therapy in meningococcal septicaemia

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Hunter, J. (1973). Archives of Disease in Childhood, 48, 233. Heparin therapy in meningococcal septicaemia. Two cases of meningococcaemia with bad prognostic signs are presented. In one child a state of disseminated intravascular coagulation and defibrinogenation was established. Heparin therapy was used early and successfully in both cases, supporting the value of early anticoagulation in the management of severe meningococcal septicaemia.

The mortality remains high in meningococcal septicaemia complicated by the Waterhouse-Friderichsen syndrome, despite the apparent improvement in the management of the severely ill child as shown by a review of the experience at the Royal Children's Hospital, Melbourne, over the years 1957 to 1970 (Table I). The role of patients with a poor prognosis (Stiehm and Damrosch, 1966). Using these criteria we have been able to identify 2 patients with poor prognostic scores, in 1 of whom evidence of disseminated intravascular coagulation was established. In both patients a satisfactory outcome was associated with early heparin treatment.

<p>| TABLE I |
| Mortality of meningococcaemia at the Royal Children's Hospital, Melbourne, 1957 to 1970 |</p>
<table>
<thead>
<tr>
<th>Years</th>
<th>Cases</th>
<th>Deaths</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1957-1959</td>
<td>56</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>1960-1964</td>
<td>30</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>1965-1970</td>
<td>27</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>113</td>
<td>12</td>
<td>11</td>
</tr>
</tbody>
</table>

disseminated intravascular coagulation in the pathogenesis of this form of irreversible shock has been suggested by a number of factors (Corrigan, Ray, and May, 1968; Hodes, 1969), including the pathological changes seen in fatal cases (Margaretten, Csavossy, and McKay, 1967; Evans et al., 1969; Fox, 1971). Laboratory evidence of intravascular coagulation and defibrinogenation has been found in fatal cases of meningococcal septicaemia (McGehee, Rapaport, and Hjort, 1967). In view of this association, heparin therapy has been used but results have been disappointing (Hitzig, 1964; Najjar and Ahmad, 1969). The failure has been attributed by some to delay in the initiation of heparin therapy. To overcome this delay we have attempted to use a combination of readily available prognostic features which may predict those

Case histories

Case 1. This 26-month-old boy was admitted with a 10-hour history of abdominal pain, vomiting, and fever, having had no previous significant illness. On admission he was stuporose, with a blood pressure of 95 mmHg systolic, but was not in peripheral circulatory failure. There were a few scattered petechiae about the mouth and on the buttock. Within 1 hour of admission his condition deteriorated with the development of periphery circulatory failure and further petechiae on the chest and abdomen. Resuscitation was started with intravenous plasma albumin, sodium bicarbonate, and hydrocortisone (45 mg/kg). On the basis of the unfavourable prognostic features, a heparin infusion was started with an immediate dose of 150 units/kg followed by 200 units/kg 6-hourly by constant rate infusion. Penicillin, methicillin, and chloramphenicol were administered intravenously and the child was digitalized and placed in oxygen.

Investigations showed a Neisseria meningitidis group C in the blood culture; normal CSF; normal serum electrolytes with a metabolic acidosis; Hb 13.1 g/100 ml, white cell count 3900/mm³, platelets 150,000/mm². Coagulation studies before starting heparin showed a partial thromboplastin time of 123 minutes (control 49 minutes), prothrombin time of 22 minutes (control 14 minutes), fibrinogen 103 mg/100 ml (normal 200 to 400 mg/100 ml), serum fibrin degradation products 1/2048 (normal 0 to 1/16), plasminogen 0.8 units.

These results confirmed the presence of intravascular coagulation, and heparin therapy was maintained for 72 hours, during which time he was given 500 ml whole fresh blood because of a progressive anaemia. 3 hours

Received 20 July 1972.
after onset of therapy the child appeared to have recovered from the shock state with an improving peripheral circulation, a blood pressure of 125 mmHg systolic, and a central venous pressure steady at 13 cm H₂O.

The subsequent course was uneventful. After heparinization for 48 hours, the fibrin degradation products had fallen to 1/16, within normal limits. Despite the adequate heparinization, there was a progressive thrombocytopenia over the first 4 days with daily platelet counts of 150,000, 24,000, 8000, 16,000, 183,000/mm³. No extension of the petechiae was observed after heparinization. Penicillin was continued for 7 days, other antibiotics being discontinued because of the blood culture result; digoxin was discontinued after the initial dose, and the hydrocortisone was gradually reduced over the subsequent week. The child subsequently required skin grafting to a small area of skin necrosis over the heel and calf.

Case 2. This 3-year-old boy presented with an 8-hour history of fever, confusion, and ataxia. On admission he was restless and disoriented with peripheral circulatory failure and hypotension (BP 80 mmHg systolic). A scattered petechial rash was noted on the trunk and thighs. Resuscitation was undertaken with plasma, sodium bicarbonate, and hydrocortisone (35 mg/kg). In view of the prognosis, a heparin infusion was started. Blood culture grew a *Neisseria meningitidis* that was also isolated from the CSF, which was otherwise normal. The serum electrolytes were normal with a metabolic acidosis. Hb 12·3 g/100 ml, white cell count 4000/mm³, platelet count 230,000/mm³. Coagulation studies were not available. He was treated with penicillin, chloramphenicol, and sulphadimidine initially, penicillin being continued for 7 days, and the other antibiotics discontinued after the results of the cultures were known. After some initial worsening of his general condition over the first 2 hours, the child showed an improvement in peripheral circulation and conscious state. 10 hours after starting treatment for shock, he had a further hypotensive collapse which responded to 100 mg i.v. hydrocortisone. Subsequent to this episode the child made a steady improvement, though remaining slightly hypotensive for 36 hours. Heparinization was undertaken on admission with an immediate dose of 150 units/kg and maintained at 100 units/kg 6-hourly by infusion. Anticoagulation was maintained for 48 hours, and during this time he was transfused with 500 ml fresh whole blood because of increasing anaemia. There was a progressive thrombocytopenia over the first 4 days (daily platelet counts of 230,000, 120,000, 66,000, 42,000, 100,000/mm³), but no other evidence of intravascular coagulation. The skin lesions showed no extension after heparinization. His subsequent course was uneventful and steroids were discontinued after 8 days.

**Discussion**

Both cases of meningococcal septicaemia described here had a poor prognosis in terms of the factors listed by Stiehm and Damrosch (1966) (Table II). The normal ESR may relate to a lowered serum fibrinogen. A review of 113 cases of bacteriologically proven cases of meningococcaemia at the Royal Children's Hospital, Melbourne, from 1957 to 1970, confirmed the prognostic value of these criteria, such that those cases with more than 3 of these features present were associated with a very high mortality (Table III). Other factors, including age, sex, thrombocytopenia, or lack of the normal eosinopenic response to infection (Hodes, Moloshok, and Markowitz, 1952), were not found to be significant in assessing prognosis. Hypokalaemia was noted at some stage in the illness of several of the fatal cases (Mauger, 1971); however, this was also observed in a number of cases with successful outcome. The use of the prognostic score was found to be more accurate than the clinical impression of the attending physician in predicting the outcome. The role of intravascular coagulation in those patients with a poor prognosis has been inferred by the study of McGehee et al. (1967) who described 19 patients with meningococcal septicaemia, 5 of whom had proven intravascular coagulation and a universally fatal outcome: in the remaining cases without evidence of intravascular coagulation only 1 death occurred. Pathological studies have further suggested the importance of intravascular coagulation in the fatal cases of meningococcal septicaemia (Margaretten et al., 1967;
Evans et al., 1969; Fox, 1971). A case of meningococcal septicaemia has recently been described with proven disseminated intravascular coagulation successfully treated with heparin despite the delay inevitable when evidence of intravascular coagulation is sought before heparinization (Willoughby, McMorris, and Goel, 1972).

The use of the platelet count, prothrombin time, and partial thromboplastin time to screen rapidly for the presence of intravascular coagulation has been suggested (Winkelstein et al., 1969). Corrigan et al. (1968) found these tests to be abnormal in 24% of septicaemic patients without intravascular coagulation and recommended the use of the platelet count, factor V assay, and the presence of fibrin split products for the diagnosis of this state. The thrombocytopenia seen in Case 1 occurred in the presence of normal fibrin split products suggesting a cause other than intravascular coagulation.

The Stiehm and Damrosch prognostic score may be used, as in the present cases, to overcome the delay in heparinization imposed by the need for laboratory diagnosis of intravascular coagulation. The factors involved in the prognostic score are readily available and enable the delineation of a group of patients at risk. Interim heparinization can be begun while awaiting the laboratory confirmation of intravascular coagulation and defibrinization. This also limits the use of heparin in patients in whom the risk of intravascular coagulation is slight.

I thank Drs. L. E. G. Sloan and D. McCreadie of the Royal Children's Hospital, Melbourne, and R. H. R. White of Birmingham Children's Hospital, for permission to publish their cases; the physicians of the Royal Children's Hospital, for the opportunity to review their experience; and Dr. A. S. McNeish, for his help in the preparation of the manuscript.

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Arch Dis Child 1973 48: 233-235
doi: 10.1136/adc.48.3.233

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