Haemorrhagic diathesis in children associated with vitamin K deficiency

SALMAN TAJ-ELDIN, LUAY AL-NOURI, AND OMAR FAKRI

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SYNOPSIS A haemorrhagic diathesis is described in infants; this is preceded and accompanied by constitutional symptoms such as fever, diarrhoea, vomiting, anorexia, and pallor. These children had a severe coagulation abnormality, due to deficiency of vitamin-K-dependent coagulation factors, and it was corrected by administration of vitamin K. No conclusion could be drawn as to the aetiology of this condition but some possible causes are discussed.

In a haemorrhagic disorder that occurs infrequently in Iraq among infants and small children, certain features are commonly encountered. The incidence is seasonal, mainly in summer and the early months of autumn; prodromal period of fever and diarrhoea commonly precedes the haemorrhagic stage; scattered haemorrhagic lesions are seen with characteristically raised indurated purplish centres surrounded by violet haloes (Fig. 1), changing to yellow when the nodular centre disappears followed by the rest of the patch; bleeding from mucous membranes may coexist; the child may be lethargic, look ill, and anorexia, vomiting, and pallor may herald and accompany the haemorrhagic phenomena. The disease may be mild or very severe, threatening life.

MATERIAL AND METHOD

During the periods March–September 1965 and March–June 1966 15 cases of the haemorrhagic disorder under discussion were admitted to the Children's Welfare Hospital, Baghdad. One child, who was severely ill, died immediately after admission before investigations could be done, and has been excluded from this series.

Standard methods were employed for routine haematological and biochemical investigations (Whitby and Britton, 1963). The qualitative tests for factors V and VII were carried out by the technique described by Macfarlane and Biggs (1955). Fibrinogen estimation was carried out by the method of Jaques (1943). Tests for fibrinolysis were done by the clot observation test as described by DeGruchy (1964). The method of Singer, Mond, Hyman, and Levy (1950) was used in the test for circulating anticoagulants. Vitamin C estimation was done according to the method of Roe and Kuether (1943).

Owing to the relatively large number of investigations on the blood and the anaemic state of the affected children, full investigations were not done on every child.

RESULTS

All the affected children were in their first two years of life (Table 1), the youngest being 3 months old.

The male/female ratio was 3/4. All children were Arabs except one who was a Kurd. All cases came from poor families. The weight of 12 children was subnormal, although not grossly so. In the remaining two it was within normal limits. The children generally looked pale and showed varying degrees of toxic manifestations such as lethargy, lack of energy, and anorexia. None of them showed jaundice, lymphadenopathy, clubbing or spooning of the finger nails. Oedema of the feet was found in one child only (case 9). No evidence of vitamin deficiency disease, including scurvy, was found clinically.

Fever was present in all except one (case 1), and ranged in duration between three and 12 days. Mild
diarrhoea preceded the appearance of the haemorrhagic lesions in all except two patients (cases 1 and 12). The diarrhoea was always of a mild nature ranging in frequency between three and eight bowel motions a day and in duration between two and 30 days. Fever and diarrhoea did not always coincide in their time of onset or duration. Vomiting occurred in eight cases and had a frequency of two to seven times a day. The haemorrhagic lesions appeared within a period of two to 10 days from the onset of the illness.

The number of haemorrhagic spots varied from two to 22. Their diameter ranged between 1/4 and 4 in. (1.25–10 cm.). The back, chest, and legs were the sites of predilection for their distribution in that order, although the face, upper limbs, abdomen, and buttocks were also affected (Fig. 2). In this series three cases had, in addition to the cutaneous lesions, other haemorrhages from mucous membranes. Two of them (cases 11 and 14) had haematuria while the other one (case 3) had conjunctival haemorrhage.

The haemorrhagic lesions were not associated with trauma and were quite spontaneous although excessive bleeding occurred at the sites of injection or venepuncture.

The respiratory, cardiovascular, and nervous systems were normal. The liver was mildly enlarged in one case while the spleen was not enlarged in all the cases. The prenatal and natal histories did not reveal significant information.

None of the children had previous haemorrhagic episodes. None had a history of insect or animal bites. Moreover the drugs taken by some of the patients were not known to be associated with disturbance of coagulation of the blood or damage to the liver. Broad-spectrum antibiotics or sulphonamides were not taken by any of the affected children.

A history of other illnesses was either absent or insignificant. Children who were 1 year old or younger were exclusively breast fed. One of the two children above 1 year of age was still partly breast fed and both of them had an inadequate, low-protein diet. The family history did not show abnormal haemorrhagic tendencies among siblings or near relatives or parents, nor were there intercurrent illnesses in them shortly before the onset of the disease in the children.

**Laboratory Investigations** Marked to a moderate anaemia was a common feature. The red blood cells were normocytic or slightly microcytic in type, with hypochromia. There was mild to moderate leucocytosis in the majority of cases (Table I). No immature white blood cells were found in the differential counts done in three cases. Bone marrow biopsy was carried out in two cases and showed only mild hyperplasia of the myeloid and erythroid elements.

Blood cultures were done in four cases and the results were negative in all. Haemagglutination inhibition tests against the antigens of Kyasanur forest disease and Sindbis were done on two sera with negative results.

Bleeding time and platelet counts were within
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<table>
<thead>
<tr>
<th>Case No.</th>
<th>Clotting Time (min.) (Lee and White)</th>
<th>One-stage Prothrombin Time (sec.)</th>
<th>Controls</th>
<th>Addition of 10% Serum</th>
<th>Using Stypven Venom (two-stage test)</th>
<th>Prothrombin (%)</th>
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<tr>
<td>1</td>
<td>10</td>
<td>360</td>
<td>18</td>
<td>135</td>
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</tr>
<tr>
<td>2</td>
<td>9½</td>
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<td>3</td>
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<td>16</td>
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<td>16</td>
<td>80</td>
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<td>6</td>
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<tr>
<td>7</td>
<td>10½</td>
<td>140</td>
<td>18</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>210</td>
<td>17</td>
<td>120</td>
<td>60 (17)</td>
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</tr>
<tr>
<td>9</td>
<td>18</td>
<td>105</td>
<td>18</td>
<td>60</td>
<td>40 (16)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>14</td>
<td>120</td>
<td>17</td>
<td>40</td>
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</tr>
<tr>
<td>11</td>
<td>16</td>
<td>120</td>
<td>16</td>
<td>70</td>
<td>30 (15)</td>
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</tr>
<tr>
<td>12</td>
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<td>480</td>
<td>18</td>
<td>215</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>9½</td>
<td>200</td>
<td>19</td>
<td>115</td>
<td>45 (17)</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>17</td>
<td>210</td>
<td>16</td>
<td>105</td>
<td>45 (17)</td>
<td>2.7</td>
</tr>
</tbody>
</table>

*Control.*

Normal limits. Whole blood clotting time was prolonged in more than half of the cases and high normal in the rest (Table II).

Serum vitamin C estimation was done in three patients (cases 12, 13, and 14) and the results were all low normal.

Tests related to liver function, including serum estimations of glutamic pyruvic transaminase, proteins, and bilirubin, serum electrophoresis and urobilinogen in urine, were done in the first 12 cases and revealed no significant abnormalities other than a slight increase in a2 globulin in four cases and hypoproteinaemia which was not associated with a marked change in the A/G ratio in 10 cases.

A xylose tolerance test was done in two cases and the results were within normal limits in both. Stool cultures were done in eight of the cases with diarrhoea, and no growth other than the ordinary E. coli was obtained, except in one case in which there was growth of Staphylococcus aureus.

The prothrombin time was markedly prolonged in all cases (Table II). Fibrinogen was present, fibrinolysis was absent, and deficiency of factor V was excluded in all the cases. Since the prothrombin time was reduced upon the addition of normal serum, deficiency of factors VII and X or both was suspected. When Russell's viper venom (Stypven) was used for the determination of prothrombin time in order to differentiate between these two deficiencies, the prothrombin time was reduced but not quite to normal indicating that both factors were deficient. The two-stage prothrombin time was estimated in three cases and prothrombin was shown to be absent in two cases and was only 2.7% in the third (Fig. 3). The thromboplastin generation test was done in four cases. Deficiency of thromboplastin formation was found in the incubation mixture containing patient's serum, aluminium-hydroxide-treated normal plasma, and platelet

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**FIG. 3.** Two-stage prothrombin time (area method of Biggs and Douglas) in the plasma of case 14 showing a prothrombin value of 2.7% from the control.
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FIG. 4. Deficient thromboplastin formation on using the patient’s serum in the thromboplastin generation test (Biggs and Douglas). --- : control; - - - - - - - : patient.

TABLE III
EFFECT NO ONE-STAGE PROTHROMBIN TIME 24 HOURS AFTER BLOOD TRANSFUSION

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Prothrombin Time before Transfusion</th>
<th>Prothrombin Time 24 Hours after Transfusion</th>
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<td>Patient</td>
<td>Control</td>
</tr>
<tr>
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<td>360</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>450</td>
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<td>4</td>
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<td>20</td>
</tr>
<tr>
<td>5</td>
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<td>16</td>
</tr>
<tr>
<td>6</td>
<td>105</td>
<td>18</td>
</tr>
</tbody>
</table>

given vitamin K₁ and synthetic vitamin K, prothrombin time was estimated 12 hours after administration also. It was normal in the case given vitamin K₁ but markedly decreased, though not normal, in the case given synthetic vitamin K (Table IV). No new haemorrhagic lesions appeared following vitamin K administration, and haematuria, which was present in two cases, cleared up within 24 hours. Rapid improvement in the general condition and disappearance of the constitutional symptoms followed.

TABLE IV
EFFECT OF VITAMIN K ON PROTHROMBIN TIME

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Prothrombin Time on Admission (sec.)</th>
<th>Type of Vitamin K Given</th>
<th>Prothrombin Time after Administration of Vitamin K</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 Hours</td>
<td>24 Hours</td>
<td>12 Hours</td>
</tr>
<tr>
<td>7</td>
<td>140 (18)</td>
<td>K₁</td>
<td>18 (18)</td>
</tr>
<tr>
<td>8</td>
<td>210 (17)</td>
<td>K₁</td>
<td>17 (18)</td>
</tr>
<tr>
<td>9</td>
<td>105 (18)</td>
<td>K₁</td>
<td>15 (20)</td>
</tr>
<tr>
<td>10</td>
<td>120 (17)</td>
<td>K₁</td>
<td>18 (18)</td>
</tr>
<tr>
<td>11</td>
<td>120 (16)</td>
<td>Synthetic vitamin K</td>
<td>16 (16)</td>
</tr>
<tr>
<td>12</td>
<td>480 (18)</td>
<td>Synthetic vitamin K</td>
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<td>200 (19)</td>
<td>Synthetic vitamin K</td>
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<tr>
<td>14</td>
<td>210 (16)</td>
<td>Synthetic vitamin K</td>
<td>16 (16)</td>
</tr>
</tbody>
</table>

*The figures between brackets refer to prothrombin time in controls.

DISCUSSION

The association between this haemorrhagic diathesis and vitamin K deficiency is obvious because of the rapid return of the one-stage prothrombin time to normal after vitamin K had been given. The raised, indurated, subcutaneous haematomas have not been described before in vitamin K deficiency, although the evolution of the colour and their association in some cases with haemorrhages in mucous membranes, together with their response to treatment with vitamin K, leave little doubt as to their haemorrhagic nature. Combined deficiencies of prothrombin, factor VII, factor IX (Christmas factor), substitute, indicating deficiency of factors IX and X or both (Fig. 4).

Studies on the parents and other siblings in the family were done in two cases and included measurement of the bleeding time, coagulation time, and prothrombin time. The results were all normal.

RESPONSE TO VITAMIN K AND TO BLOOD TRANSFUSION

Blood transfusion, 10 ml./lb. of body weight, was given to the first six cases (1–6), before vitamin K was tried, and the results showed that prothrombin time was only slightly reduced 24 hours after blood transfusion (Table III). Prothrombin time, however, eventually returned to normal in a period of six to nine days. Improvement in the general condition was also not appreciable immediately following blood transfusion.

Vitamin K₁ (Konakion-Roche), 10 mg., was given to four patients while synthetic water-soluble vitamin K (Synkavit-Roche), 10 mg., was given to the other four intramuscularly. In all cases the prothrombin time returned to normal in 24 hours (Table IV).

In one case of each of the two groups that were
and factor X are shown to coexist in vitamin K deficiency (Douglas, 1958), a multiple deficiency similar to that found during coumarin and indandione therapy (Naeye, 1965; Sise, Kimball, and Adanis, 1955; Douglas and Mair, 1958). Such anticoagulants were not taken by the children under discussion or by their mothers. The tests for circulating anticoagulants were also negative.

Similar combined deficiencies were reported as rare congenital anomalies (Newcomb, Matter, Conroy, DeMarsh, and Finch, 1956; Biggs, 1956). A congenital aetiology in our cases is unlikely because of the constant association of the haemorrhagic episodes with constitutional symptoms, the negative family history of any haemorrhagic tendency, and the normal results in haemostatic tests of the parents and the siblings. Furthermore the affected children were completely cured.

Liver function tests did not show evidence of liver damage in these patients; furthermore there was no demonstrable deficiency of factor V in any case (Owren, 1949; Stefanini, 1950). The complete and rapid correction of the prothrombin time with vitamin K is another strong argument against liver damage (Unger and Shapiro, 1948).

Since in no case in this series antibiotics were used, the vitamin K deficiency cannot be attributed to sterilization of the alimentary tract which may be caused by their prolonged use with consequent lack of synthesis of vitamin K (Herfort and Standand, 1948; Dearing, Mann, and Needham, 1952). Steatorrhoea and biliary obstruction, which can also lead to vitamin K deficiency, were excluded clinically and by laboratory tests.

Deficient intake of the vitamin may play a part since milk, which formed the only or the main diet of our patients, is deficient in vitamin K (Whitby and Britton, 1963). The mildly prolonged prothrombin time, sometimes associated with petechial haemorrhages, in certain cases of kwashiorkor was attributed to this factor (Merskey and Hansen, 1957). Intestinal hurry with deficient absorption of vitamin K can occur in some cases of gastro-enteritis leading in some cases to prolongation of prothrombin time (Rapoport and Dodd, 1946; Hallman and Kauhtio, 1949). In our patients only mild diarrhoea occurred in the majority of cases and not in all of them and was usually of short duration, while the prolongation of the prothrombin time was much greater than that described in gastro-enteritis. Moreover, no haemorrhagic lesions of the type described in our patients are observed in gastro-enteritis.

Many of the clinical features in our cases, such as fever, vomiting, mild diarrhoea, anorexia, toxic appearance, and the mild leucocytosis, suggest an infective aetiology. Yet bacterial and viral studies done on the blood and the search for any source of infection and stool bacterial cultures did not reveal any causative factor.

It is possible that these patients have a critically low vitamin K level resulting from its low intake. Any infection, possibly an intestinal viral one, could have caused decreased vitamin K synthesis in the intestine by depressing the normal intestinal flora, thus leading to decreased formation of prothrombin and the other vitamin K-dependent coagulation factors. The seasonal incidence and the common association of the haemorrhagic disorder with fever and diarrhoea are in keeping with this assumption. Further research based on this hypothesis will be the subject of a future communication.

A special debt of gratitude is due to Professor A. S. Douglas who read this paper and made some very valuable comments on it. Our thanks go also to Professor A. Kekwick, Dr. R. Dobbs, Professor J. F. Wilkinson, and Professor M. Jalili for their help, and to Professor F. J. Collard and his staff for doing the virological tests at his Department. Dr. S. Sarraj and Mr. A. Baki gave us technical assistance.

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