Serum alpha₂-macroglobulin, transferrin, albumin, and IgG levels in preeclampsia

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SYNOPSIS A radial immunodiffusion technique has been used to measure levels of four serum proteins in preeclampsia with or without proteinuria and in normal pregnant and non-pregnant controls. In preeclampsia unaccompanied by proteinuria, albumin and transferrin levels are similar to those found in the normal pregnant controls, but there are significant falls in alpha₂-macroglobulin and IgG. When preeclampsia is accompanied by proteinuria there is a marked fall in albumin and an increase in alpha₂-macroglobulin. Since alpha₂-macroglobulin has antiplasmin activity it is possible that increased levels of this protein in preeclampsia accompanied by proteinuria contribute to the intravascular coagulation which has been described in this disorder.

Both in pregnancy and the nephrotic syndrome increased levels of serum alpha₂-macroglobulin have been reported (Schumacher and Schlumberger, 1963; Schultze and Schwick, 1959). We therefore thought it would be of interest to determine the serum alpha₂-macroglobulin levels in preeclampsia, a complication of pregnancy which bears a certain similarity to the nephrotic syndrome. For comparison the serum levels of transferrin, IgG, and albumin have also been measured to demonstrate changes due to factors such as haemodilution.

We report here the serum levels of alpha₂-macroglobulin, transferrin, IgG, and albumin, assayed by a radial immunodiffusion technique, in preeclampsia and in matched normal pregnant and non-pregnant controls.

Subjects and Methods

Sera were obtained from four groups of patients: (1) preeclampsia with proteinuria (13 cases); (2) preeclampsia without proteinuria (13 cases); (3) normal pregnant (26 cases); (4) non-pregnant (26 cases). Preeclampsia was defined as hypertension (blood pressure higher than 140/90 mm Hg) on two or more separate occasions after 28 weeks of pregnancy in patients whose blood pressure was less than 140/90 mm Hg in the first trimester. Most of the patients had oedema. Preeclampsia with proteinuria was diagnosed when proteinuria was detected for the first time after 28 weeks of pregnancy and was not due to urinary tract infection, preexisting renal disease, or contamination with vaginal discharge. For comparison 13 sera were selected from 37 obtained from preeclamptic patients without proteinuria: the cases were chosen to match the first group as closely as possible (see Table) with respect to age (within two years), parity (primiparous or multiparous), and duration of pregnancy (within five weeks except one in which the difference was 10). For each preeclamptic case a control serum was obtained from a normal pregnant woman matched for age (within two years), parity, and duration of pregnancy (within four weeks except for two where the difference was seven and eight weeks). An additional control group consisted of 26 patients attending a gynaecological outpatient clinic and matched for age with the preeclamptic patients. The normal pregnant and non-pregnant controls used in this experiment were selected from a group of 37 described in a
previous communication (Horne, Howie, Weir, and Goudie, 1970). The sera were stored at −20°C for up to six months before assay.

The assay of the serum proteins was carried out using a radial immunodiffusion technique (Horne et al, 1970) similar to that described previously. To minimize the effects of interplate variation (Thompson, Horne, Steele, and Goudie, 1969) matched cases of preeclampsia, together with the pregnant and non-pregnant controls, were always tested in duplicate on the same assay plate and the results read by an observer who did not know the arrangement of the sera within each plate. The arithmetic mean of the two readings was used in all calculations. The ‘absolute values’ of the measured proteins were determined from the calibration curves with solutions of a freeze-dried, reconstituted pooled human serum containing 3, 6, 12, and 18 g protein per 100 ml and standardized with reference to a serum (Behringwerke AG) containing specified amounts of the particular protein.

Results

The serum protein levels in preeclampsia and in matched normal pregnant and non-pregnant controls is given in the Table which also shows where statistically significant differences between groups have been found by the Student's t test.

A more detailed comparison of α2-macroglobulin levels is shown in the Figure. In normal pregnancy compared with non-pregnant controls there are significant increases in the levels of α2-macroglobulin (+37%) and transferrin (+53%) and falls in the levels of albumin (−31%) and IgG (−20%).

Comparing preeclampsia without proteinuria with normal pregnancy there are significant falls in the levels of α2-macroglobulin (−19%) and in IgG (−16%), but no significant difference in the transferrin and albumin levels. However, comparison of the two groups of preeclamptic patients shows a significant increase (+55%) in the α2-macroglobulin level and a significant fall in the albumin level (−21%) associated with the presence of proteinuria. No significant difference between the transferrin or IgG levels is observed.

Discussion

Our findings in preeclampsia relating to albumin are similar to those of other authors (Spetz and Brody, 1967; Hönger, 1966), although we do not know of a previous demonstration that proteinuria in this condition is associated with more profound hypoalbuminaemia. Hönger (1966) has found increased catabolism of albumin in preeclampsia; presumably the resulting fall in plasma albumin is further accentuated by proteinuria when present. The fall in IgG in preeclampsia is in keeping with the electrophoretic findings of

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Cases</th>
<th>Mean Age (yr)</th>
<th>Duration of Pregnancy (wk)</th>
<th>Mean (± SD) Serum Levels (mg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>α2-Macroglobulin</td>
</tr>
<tr>
<td>1 Preeclampsia with</td>
<td>13</td>
<td>27.7</td>
<td>35.2</td>
<td>ab</td>
</tr>
<tr>
<td>proteinuria</td>
<td></td>
<td>(range 18-38)</td>
<td>(range 30-40)</td>
<td></td>
</tr>
<tr>
<td>2 Preeclampsia without</td>
<td>13</td>
<td>27.9</td>
<td>37.0</td>
<td>ac</td>
</tr>
<tr>
<td>proteinuria</td>
<td></td>
<td>(range 18-41)</td>
<td>(range 34-40)</td>
<td></td>
</tr>
<tr>
<td>3 Normal pregnancy</td>
<td>26</td>
<td>27.6</td>
<td>36.8</td>
<td>d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(range 18-43)</td>
<td>(range 32-40)</td>
<td></td>
</tr>
<tr>
<td>4 Non-pregnancy</td>
<td>26</td>
<td>27.6</td>
<td>—</td>
<td>e</td>
</tr>
</tbody>
</table>

Table Serum protein levels in preeclampsia and in matched normal pregnant and non-pregnant controls

a P < 0.005 b P < 0.025 c P < 0.05 d P < 0.0025
e P < 0.0005 f P < 0.0025 g P < 0.0005 h P < 0.0005
i P < 0.01 j P < 0.05 k P < 0.005
Some (Mack, 1960) but not all authors (Spetz et al, 1967).

High $\alpha_2$-macroglobulin levels in preeclampsia with proteinuria do not appear to have been encountered previously. Mack (1960) and Spetz and Brody (1967) found normal $\alpha_2$-globulin levels in preeclampsia but they used the less discriminating technique of filter paper electrophoresis and did not separate preeclampsia into two groups according to the presence or absence of proteinuria. Wardle and Menon (1969) did not find any increase in $\alpha_2$-macroglobulin levels in preeclampsia accompanied by proteinuria compared with normal pregnancy, but details of their radial immunodiffusion technique are not given. Since our findings are at variance with those of the above authors they require further confirmation in carefully controlled studies. In a previous communication (Horne et al, 1970) we showed that administration of combined oestrogen and progestogen oral contraceptives results in increases in $\alpha_2$-macroglobulin, transferrin, and IgG, and suggested that the raised levels of $\alpha_2$-macroglobulin and transferrin in normal pregnancy might be due to raised blood levels of these hormones. Our findings in preeclampsia without proteinuria of lower levels of $\alpha_2$-macroglobulin, transferrin, and IgG than expected in normal pregnancy are consistent with the effects of diminished production of oestrogen and/or progestogen, and there is some indication of decreased production of oestrogens in preeclampsia according to the severity of the disease (Klopper, 1968).

Severe preeclampsia resembles the nephrotic syndrome in showing hypoalbuminaemia, proteinuria, and oedema, and this resemblance is further emphasized by high $\alpha_2$-macroglobulin levels often found in both conditions. The factors causing raised $\alpha_2$-macroglobulin levels in these conditions are obscure. Hypoalbuminaemia does not appear to be a cause since we failed to demonstrate an inverse correlation between serum albumin and $\alpha_2$-macroglobulin in the cases presently under study. The lack of a comparable rise in transferrin is against an oestrogen and/or progestogen effect on $\alpha_2$-macroglobulin in preeclampsia with proteinuria and there is no evidence that these hormones are increased in severe preeclampsia.

Intravascular thrombosis in the glomerulus (Morriss, Vassalli, Beller, and McCluskey, 1964) and in the spiral arteries of the placental bed (Robertson, Brosens, and Dixon, 1967) are features of preeclampsia. Impaired fibrinolysis due to diminished plasminogen activator is well known in normal pregnancy (Wardle et al, 1969; Bonnar, McNicoll, and Douglas, 1969) but there is no apparent difference in fibrinolytic activity between normal pregnancy and preeclampsia (Wardle et al, 1969). In view of the antiplasmin activity of $\alpha_2$-macroglobulin (Williams, 1969; Schultz, Heimbucher, Heide, Haupt, Stoëriko, and Schwick, 1963; Steinbuch, Quentin, and Pejauddier, 1965; Ganrot, 1967) it would be of interest to know whether intravascular thrombosis is especially found in preeclamptic patients who have proteinuria or raised $\alpha_2$-macroglobulin levels. If raised $\alpha_2$-macroglobulin levels really contribute to intravascular thrombosis in preeclampsia they might be expected to cause similar effects in the nephrotic syndrome. The only well known thrombotic association of the nephrotic syndrome is renal vein thrombosis, but the relationship of this to membranous glomerulonephritis (Lancet, 1969) and amyloid disease of kidney (Heptinstall, 1967) is not fully understood.

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References

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