Significance of platelet antibodies in neonatal thrombocytopenic purpura affecting a pair of siblings

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SYNOPSIS A pair of siblings, both of whom had neonatal thrombocytopenic purpura, are described. During the first pregnancy, the mother was given chlorothiazide and the implications of this therapy are considered. At the end of the second pregnancy a platelet iso-antibody was detected in the maternal serum. The possible reason for not detecting this antibody in the serum of the second child is considered.

Evidence of the transplacental transfer of red cell antibodies is well established, but proof that platelet antibodies behave in the same way has not been so quickly forthcoming despite the fact that thrombocytopenic purpura in the newborn was reported as long ago as 1873 by Dohrn. Nevertheless, since 1950, with some improvement of techniques for the detection of platelet antibodies, reports have come from various workers describing the presence of such antibodies in the sera of infants suffering from neonatal thrombocytopenic purpura, and also in the sera of their mothers. Cases fall into two groups: those in which the mother suffers from idiopathic thrombocytopenic purpura and transmits her platelet auto-antibody to her foetus, and those in which the mother is apparently normal, but possesses a platelet iso-antibody, developed presumably as a result of pregnancy or transfusion. In either case, the effect on the child is the same, there being thrombocytopenia, with or without purpura, which disappears as the amount of maternal platelet antibody diminishes in the child's circulation.

In this paper, we wish to report the case histories of two brothers who each became purpuric shortly after birth and later died. Menzies (1964) has already referred to the first of these two children in his paper on a 'Controlled trial of chlorothiazide in treatment of early pre-eclampsia'. The serum of the second of these two children and of the mother were examined for possible presence of platelet antibodies, but such tests were not performed during or after the first pregnancy.

Perhaps as important as the detection of platelet antibodies in the second pregnancy was the fact that the mother received chlorothiazide for hypertension during the first pregnancy. Recently, Rodriguez, Leink, and Hiller (1964) reported the development of neonatal thrombocytopenia associated with the ante-partum administration of thiazide drugs.

CASE HISTORIES

Mrs. A., aged 27 years, was a healthy woman at the time of her first pregnancy. Her previous medical history was not relevant and at no time had there been evidence of a bleeding tendency. She and her husband are not blood relations.

CASE 1 Simon A., the first child of Mrs. A., was born on 3 October 1961, following an uncomplicated vertex delivery at 34 weeks' gestation, the birth weight being 4 lb. 10 oz. (2·1 kg.). The mother had had mild pre-eclamptic toxaemia for which she was treated with chlorothiazide from the twenty-third week, but her condition deteriorated rapidly shortly before delivery, with the development of albuminuria, oedema, and a rise of blood pressure to 140/110 mm. Hg; at no time did she show evidence of thrombocytopenia or purpura.

From the time of delivery, extensive purpura, confluent in places, spread over the baby's trunk, limbs and in the mouth, but no fresh petechial haemorrhage could be observed after 2 hours of age. In addition, respiratory difficulty was present from birth and became progressively more severe.
Investigations shortly after birth showed haemoglobin 11·9 g./100 ml. (81%); W.B.C. 17,000/c.mm. with a normal differential count; prothrombin time 15·5 seconds, control 11·6 seconds; blood group O Rhesus positive, direct antiglobulin (Coombs) test negative; platelets less than 1,000/c.mm.; serum bilirubin 2·9 mg./100 ml.

Potassium menaphthosulphate (Vikastab), 3 mg., was given on the day of delivery and steroid therapy was begun at two hours. At 12 hours, because of increasing irritability and the possibility of intracranial haemorrhage, he was given a transfusion of 95 ml. of fresh donor blood.

On the second day, no platelets could be seen in the peripheral blood, either in a stained smear or in a wet preparation. Severe respiratory distress with cyanosis was now present, there was marked irritability on handling, and the fontanelle tension was increased. Subdural taps were negative, but lumbar puncture revealed a grossly bloodstained cerebrospinal fluid under pressure, the supernatant being deeply xanthochromic.

Respirations subsequently became increasingly laboured and the infant died, aged 53 hours.

NECROPSY FINDINGS (DR. W. G. SPECTOR) There were numerous subserous haemorrhages over the lungs, heart, and intestines with some bleeding into the renal pelvis and bladder mucosa. There was extensive bilateral haemorrhage over the surface of the brain excavating the temporoparietal lobes on the left-hand side. The lungs were congested and sank in formol saline; on microscopy they showed massive intra-alveolar haemorrhage, oedema, and very extensive hyaline membrane formation. No megakaryocytes could be seen in a smear of tibial marrow taken within 10 minutes of the infant’s death. The spleen was slightly enlarged, dark and firm.

CASE 2 Paul A., the second child of Mrs. A. (see Fig. 1), was born on 19 August 1963, following a normal pregnancy and delivery at 37 weeks and weighed 7 lb 7 oz. (3-380 kg.). In the first hour after delivery, he rapidly developed extensive purpura and subcutaneous ecchymoses. Later, there was slight bleeding per rectum. Large fontanelle-like cranial defects were present over the temporoparietal areas above both ears. The initial investigations were: haemoglobin 20·7 g./100 ml. (140%), platelets 42,000/c.mm., bleeding time 7 minutes, clotting time 2 minutes 2 seconds.

Steroid therapy was commenced at once, using parenteral hydrocortisone, 100 mg. daily. Prednisolone, 20 mg., was substituted on the eighth day and the dosage gradually reduced to 7·5 mg./day. The platelet count, after dropping to 22,000/c.mm. on the third day, varied from 60,000 to 200,000/c.mm. The only possible further episode of haemorrhage was an unexplained swelling of the left calf on the fifth day, which subsided spontaneously. At no time was the fontanelle tension increased, but examination of the cerebrospinal fluid on the ninth day showed a pale straw-coloured fluid with a protein content of 106 mg./100 ml. suggesting previous intracranial haemorrhage.

The skull circumference, 36 cm. at birth, increased steadily until it was 37·5 cm. on the nineteenth day, and on the twenty-second day burr hole ventriculography was performed (Mr. B. J. Harries). The cortex was thinned to 1-2 mm. thickness over the lateral ventricles. A very large multilocular porencephalic cyst communicated with the temporal horn of the right ventricle and almost completely replaced the right hemisphere. The aqueduct and fourth ventricle were not demonstrated. Ventricular drainage was temporarily instituted, but abandoned after four days.

Subsequently, the baby continued to feed well, but his skull enlarged progressively until the circumference was 42·6 cm. He died suddenly on the fiftieth day.

NECROPSY FINDINGS (DR. J. WIGGLESWORTH) The brain was markedly hydrocephalic with bilateral porencephalic cysts, very large on the right. There was evidence of old small subarachnoid haemorrhages around the base of the brain. The bone marrow of a lumbar vertebra and femur appeared normal, except that it did not contain megakaryocytes. The adrenals were markedly atrophic, but the other systems appeared normal. The spleen weighed 9 g. and was normal both macroscopically and histologically.

FIG. 1. Paul A. (case 2) showing purpura and ecchymoses.

TECHNIQUES

PLATELET COUNTING A wet preparation was examined in each case, and the ratio of platelets to red cells enumerated after the total red cell count had been performed.
PLATELET AGGLUTINATION  Tests were performed independently by K.L.G.G. and W.J.J., each worker using both the method of Dausset, Colin, and Colombani (1960) and a tube technique.

INDIRECT ANTIGLOBULIN CONSUMPTION TESTS  The method of Dausset and Brecy (1958) was used by K.L.G.G. and W.J.J., platelets being obtained from healthy blood donors, the mother or father as indicated.

RESULTS

Details of platelet counts are recorded in the case histories.

Platelet agglutinins were not detected either in the serum of the mother or of Paul A. Simon A. was not tested. Platelets of healthy donors, of the mother, and of the father were used in each case.

Antiglobulin consumption tests were performed and results showed the presence of antibodies in the mother’s serum to the father’s platelets and to pooled donor platelets, but not to her own platelets (Table I).

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<td>W.J.J.</td>
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DISCUSSION

The possible connexion of neonatal thrombocytopenia with the maternal administration of thiazide drugs was not appreciated until the publication of the paper by Rodriguez et al. (1964) to which reference has already been made above. It seems likely that Simon A. developed thrombocytopenia because of the administration of chlorothiazide. During the second pregnancy no such drug was used, but Mrs. A. may have been sensitized by her first child, developing an iso-platelet antibody which we were able to detect later. The possible relationship between the development of an iso-platelet antibody detected during the second pregnancy and the administration of chlorothiazide during the first is difficult to determine. It seems unlikely that the appearance of two different pathologies can be entirely coincidental and one wonders if the mother, while receiving the drug, was rendered more susceptible to the foetal platelet antigens, consequently developing a platelet antibody that was detected during the second pregnancy, or whether, in both cases the thrombocytopenia was due to her platelet iso-antibody.

Table I shows that the iso-platelet antibody detected in the mother’s serum was capable of reacting with an antigen on the husband’s platelets but not on her own. To obtain platelets for the tests a large volume of blood is required, so for this reason it was not possible to study the reaction of baby Paul’s platelets in the presence of the maternal antibody. It may at first appear surprising that no free antibody was detected in the serum of this child, but, as has been shown by Wiel, Wiel-Dorfmeyer, and Loghem (1961) in cases of idiopathic thrombocytopenic purpura, it is not uncommon for all the platelet antibody to be fixed to the platelet with consequently none free in the serum. Testing for platelet antibodies in two independent laboratories, and obtaining identical results, does a great deal, we believe, to strengthen the validity of our findings.

Pearson, Shulman, Marder, and Cone (1964) have recently reported a series of cases of iso-immune neonatal thrombocytopenic purpura and have included a very complete review of the literature since 1945. In all, they record 55 cases, platelet antibodies having been sought in all but four of them. Of these sera examined, 20 out of 51 (39%) were found to possess iso-antibody. They also reported the occurrence of intracranial haemorrhage in at least six cases. Moreover, these authors reported the occurrence of hydrocephalus in children of one of the families they examined, which thus resembled Paul A. in this respect. Pearson et al. (1964) thought that steroid therapy to the infant might shorten the duration of thrombocytopenia, but it did not appear to help in the case of Paul A.

We are grateful to Dr. B. E. Schlesinger and Dr. L. Strang for permission to study cases 1 and 2 respectively, and to the Haematology Department of University College Hospital for performing the platelet counts, to Dr. W. G. Spector for performing the necropsy on case 1 and to Dr. J. Wigglesworth for that of case 2. We wish to thank Dr. W. d’A. Maycock of the Lister Institute, Elstree, for supplying some of the platelets used, and the Photographic Department of University College Hospital for the photograph of case 2.

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K. L. G. Goldsmith, W. J. Jenkins, E. S. Mucklow, and I. C. S. Normand