Infective hepatitis and acquired hypogammaglobulinaemia during pregnancy with complete recovery

BRIAN J. PROUT

Ph.D., M.B., B.S., M.R.C.P.(Lond.)

*Senior Registrar in Medicine,
Radcliffe Infirmary, Oxford*

VINCENT MARKS

M.B., B.Ch., M.R.C.P.Ed., M.C.Path.

*Consultant Pathologist,
Epsom District Hospital, Surrey*

SINCE the finding by Bruton in 1952 of the absence of γ -globulin in the serum of an 8-year-old boy, and the demonstration that the patient was unable to synthesize antibody in response to antigenic stimulation, there has been an enormous amount of literature (Good *et al.*, 1962) on what has been labelled the *antibody-deficiency syndromes* (Barandun *et al.*, 1961; Soothill, 1967). The syndromes have now been classified into six main groups (Rosen & Janeway, 1966), the most usual clinical manifestation being susceptibility to bacterial infections notably with Gram-positive organisms.

It has been stated that such patients are particularly susceptible to homologous serum hepatitis (Good & Page, 1960) and to infection with the virus of infective hepatitis (Squire, 1962). Many of the traditional tests of 'liver function', e.g. thymol and zinc sulphate turbidities, cephalin cholesterol and colloidal gold tests, A : G ratios and electrophoretic pattern, depend upon the changes in plasma protein composition. The absence of such alterations in hypogammaglobulinaemia may lead to difficulties of diagnosis as in a patient with infective hepatitis described here in whom pregnancy existed as a further complication. This combination of clinical features has not, to our knowledge, been previously recorded.

Case report

The patient, B.L., a 17-year-old unmarried girl, was admitted to hospital on 7 January 1965, with a 2-week history of jaundice associated with severe anorexia, nausea, vomiting and right hypochondrial abdominal pain. There was no history of the ingestion of possible hepato-toxic substances; she had not had any recent injections and there was nothing to suggest exposure to leptospirosis. Her previous health had always been

good with no susceptibility to infections, and there was no history of previous episodes of jaundice or abdominal pain.

On examination, she was drowsy, deeply jaundiced and mildly pyrexial (99–100°F). There was a palmar erythema and spider naevi were present, but there was neither tremor of the hands nor other abnormal neurological signs. The liver was tender but not enlarged and the spleen was impalpable. Breast activity and uterine enlargement was consistent with a 20-week pregnancy. There was no evidence of pre-eclamptic toxæmia. The blood pressure was 100/55 mmHg, and urinalysis showed no proteinuria.

Investigations. Chest X-ray was normal and WR negative. On admission the stools were pale and the urine bile-stained. Apart from slight proteinuria on one occasion there was no evidence of renal dysfunction. Blood urea was normal or low throughout the illness. Haemoglobin was 14.6 g/100 ml (100%), WBC 9100/mm³ with normal differential; ESR was 7 mm/hr (Westergren) and the Paul-Bunnell negative. One month after admission the haemoglobin concentration was down to 7.9 g/100 ml (54%) and there was a polymorphonuclear leucocytosis, 12,000/mm³. The reticulocyte count was 3%. The results of routine liver function tests are shown in Table 1. The one-stage prothrombin time (thrombotest) was 30% of normal. There was gross hypogammaglobulinaemia by both quantitative cellulose acetate electrophoresis and an immunochemical technique (Table 2). The patient's red cells were group O, but the anti-A isoagglutinin titre was only 1 : 4 and anti-B isoagglutinins were undetectable.

Progress. Feeding with a high protein and carbohydrate and low fat diet, supplemented with liquid glucose and fructose drinks, was instituted. Treatment with prednisone 40 mg/day, ampicillin

1 g/day, vitamin K 10 mg/day and parenteral vitamins was commenced on 9 January 1965. γ -Globulin (0.5 g) was given by intramuscular injection on 16 January 1965.

Jaundice deepened during the 1st week of hospital admission and gradually lessened over the next 8 weeks. She was confined to bed while bilirubinuria persisted. After a further week of observation she was transferred to the convalescent ward for 3 weeks.

Therapeutic abortion was considered at one stage but thought not to offer any advantage to the patient, who was, in any case, in no state to withstand an anaesthetic or abdominal hysterotomy.

Pregnancy continued normally and when discharged from hospital 10 weeks after admission

the patient was clinically well and 'liver function tests' had returned almost to normal though hypogammaglobulinaemia persisted (Tables 1 and 2).

A normal healthy male infant was delivered at term, but she showed on qualitative cellulose acetate electrophoresis the anticipated gross hypogammaglobulinaemia; the concentration measured by a quantitative immunochemical technique was 183 mg/100 ml.

After delivery, the patient returned to work in excellent health and on re-examination 2 months after delivery serum electrophoresis showed a significant rise in γ -globulin. This was confirmed on two subsequent occasions (Table 2) on one of which the anti-A isoagglutinin titre was 1 : 128 and the anti-B isoagglutinin titre 1 : 16. Further

TABLE 1
Empirical liver function tests during and after the patient's illness

Date	Total bilirubin (mg/100ml)	Alkaline phosphatase (K.A. units)	SGOT (S.F. units)	SGPT (S.F. units)	Serum cholesterol (mg/100 ml)	Total protein (g/100 ml)	Thymol turbidity (units)	Zinc sulphate turbidity (units)	Urea (mg/100 ml)	ESR (mm/hr)	Hb (g/100 ml)
1964											
28 December	9.9	25	1150	1450	285	5.7	1	1		4	15.5
1965											
1 January	14.3	32	950	910	265	4.6	1	1			
7 January	10.8	27	420	390	240	4.6	1	1		7	
15 January	21.0	22	280	210	215				8		
18 January	11.3	21	141	110	205	3.8	1	1			7.9
21 January	10.8	22	140	105	290	3.9	1	1			9.8
25 January	7.1	19	200	170	230	4.3	1	1		17	8.2
29 January	5.8	22	117	104	260	5.1	1	1			
5 February	2.6	32	75	72	260	5.0	1	1			
11 February	1.3		37	39	255		1	1		12	9.5
15 February	1.2	24	37	28	269	4.8	1	1			
1 March	0.6	16	20	18	256	4.5	1	1			
31 May	<0.5	18	28	26	290	6.1	1	1			
3 September	<0.5	17	34	35	235	6.1	1	1			15.0
25 November	<0.5	12	7	9	180	6.0	1	2	34		

TABLE 2
Plasma proteins during and after the patient's illness

Date (1965)	Total plasma proteins (g/100 ml)	Albumin* (g/100 ml)	Globulin (g/100 ml)*				A/G ratio
			α_1	α_2	β	γ	
5 January	4.8	3.8	0.2	0.3	0.3	0.2 (195/mg†)	3.9
18 January	3.8	2.7	0.2	0.4	0.3	0.2 (215 mg†)	2.3
21 January	3.9	2.8	0.2	0.4	0.4	0.1	2.8
25 January	4.3	2.8	0.2	0.5	0.5	0.3 (330 mg†)	2.1
29 January	5.1	2.9	0.4	0.8	0.8	0.2	1.5
15 February	4.8	2.7	0.3	0.8	0.8	0.2	1.1
1 March	4.5	2.6	0.4	0.7	0.8	0.2	
31 May	6.1	3.7	0.3	0.7	0.9	0.5	1.5
3 September	6.1	3.7	0.3	0.7	0.9	0.5	1.5
25 November	6.0	3.3	0.3	0.7	1.0	0.7	1.2

* Quantitative cellulose-acetate electrophoresis.

† IgG measured immunochemically.

follow-up was prevented by loss of contact with the patient.

The plasma proteins of both the patient's mother and sister were within normal limits.

Discussion

The interest of the present case lies not only in the rarity but in the problem of differential diagnosis it presented.

There are many causes of jaundice in pregnancy but infective hepatitis is the commonest (Sherlock, 1961). Since identification of the causative agent of infective hepatitis is not at present practicable, diagnosis can often only be made by exclusion. This is greatly facilitated by empirical tests of liver function which yield a highly characteristic pattern of abnormalities in the majority of cases (Hanger, 1960; McLagen, 1964). The course of the patient's illness and her subsequent progress leave little doubt that she was suffering from infective hepatitis, occurring during pregnancy and against a background of primary acquired hypogammaglobulinaemia (Good *et al.*, 1960; Paterson, Cooper & Good, 1965; Rosen & Janeway, 1966), although there was some doubt about this initially.

A low ESR and normal thymol and zinc sulphate turbidities together with the low serum γ -globulin content pointed more towards drug or poison induced hepato-necrosis than to an infective lesion (McLagen, 1964), especially as there was reason, albeit a tenuous one, for the use of an abortifacient.

The possibility of idiopathic jaundice of pregnancy was also considered. This condition, though sometimes accompanied by and associated with toxæmia, is not invariable so and, unlike infective hepatitis, is relieved only by termination of pregnancy (Nixon *et al.*, 1947).

The diagnosis of hypogammaglobulinaemia was established in this case on the basis of: (1) abnormally and persistently low plasma γ -globulin levels, (2) their failure to rise during the course of infective hepatitis normally a powerful stimulus to γ -globulin production (Rafsky *et al.*, 1950), and (3) an extremely low isoagglutinin titre in a subject with blood group O.

Pregnancy has been said to affect the course of infective hepatitis adversely (Nixon *et al.*, 1947) possibly because protective nutriment is diverted to the foetus. There is no evidence, however, that in previously normally nourished individuals pregnancy predisposes to infective hepatitis, increases its severity or is especially hazardous to the foetus (Sherlock, 1961).

It has been suggested that patients with hypogammaglobulinaemia whose normal resistance to most virus infections is well established are never-

theless more liable to infective (Squire, 1962) and serum (Good & Page, 1960) hepatitis than normal subjects. However, the evidence for this is tenuous as the total number of cases in which the association of hypogammaglobulinaemia with acute or chronic liver disease has been reported (Squire, 1962; Good & Page, 1960; Girard *et al.*, 1962) is small, even though serum electrophoresis is now routinely carried out as part of the battery of liver function tests used in the differential diagnosis of jaundice.

Illness in the present case was severe, but not more so than may be encountered in cases of infective hepatitis uncomplicated by hypogammaglobulinaemia and lends no support to the suggestion that when infective hepatitis occurs in the hypogammaglobulinaemic it is not only unusually profound but also leads inevitably to cirrhosis and death (Good & Page, 1960).

Summary

A patient with infective hepatitis and primary acquired hypogammaglobulinaemia during pregnancy is described. Pregnancy progressed to term with spontaneous delivery of a healthy child who also had a low γ -globulin level returning spontaneously to normal. The relationship of infective hepatitis and hypogammaglobulinaemia is discussed.

Acknowledgments

We wish to thank A. W. W. B. Woods for permission to study this case, and Dr J. Kohn for performing immunochemical estimations of γ -globulin.

References

- BARANDUN, S., STAMFELI, K., SPENGLER, G.A. & RIVA, G. (1961) Die Klinik des Antikörpermangelsyndroms. *Helvet. med. Acta*, **26**, 163.
- BRUTON, O.C. (1952) Agammaglobulinemia. *Pediatrics*, **9**, 722.
- GIRARD, M., BEL, A., COULOT, M. & REVILLARD, J.P. (1962) Evolution cirrhogène d'une hépatite virale sur terrain agammaglobulinémique. *Arch. Mal. Appar. dig.* **51**, 1404.
- GOOD, R.A., KELLY, W.D., ROTSTEIN, J. & VARCO, R.L. (1962) Immunological deficiency diseases. *Progr. Allergy*, **6**, 187.
- GOOD, R.A. & PAGE, A.R. (1960) Fatal complication of virus hepatitis in two patients with agammaglobulinemia. *Amer. J. Med.* **29**, 804.
- GOOD, R.A., ZAK, S.J., CONDIE, R.M. & BRIDGES, R.A. (1960) Clinical investigations of patients with agammaglobulinemia and hypogammaglobulinemia. *Pediat. Clin. N. Amer.* **7**, 397.
- HANGER, F.M. (1960) Liver function tests. *Med. Clin. N. Amer.* **44**, 681.

- McLAGEN, N.F. (1964) *Biochemical Disorders in Human Disease*, 2nd edn (Ed. R. H. S. Thompson and E. J. King). Churchill, London.
- NIXON, W.C.W., EGELI, E.S., LAQUER, W. & YAKYA, O. (1947) Icterus in pregnancy—A clinico-pathological study including liver biopsy. *J. Obstet. Gynaec. Brit. Emp.* **54**, 642.
- PETERSON, R.D.A., COOPER, M.D. & GOOD, R.A. (1965) The pathogenesis of immunological deficiency disease. *Amer. J. Med.* **38**, 579.
- RAFSKY, H.A., WEINGERTEN, M., KRIEGLER, C.I., STERN, K.G. & NEWMAN, B. (1950) Electrophoretic studies in liver disease. *Gastroenterology*, **14**, 29.
- ROSEN, F.S. & JANEWAY, C.A. (1966) The gamma globulins. III. The antibody deficiency syndromes. *New Engl. J.* **275**, 709.
- SHERLOCK, S. (1961) *Disease of the Liver and Biliary System*, 2nd edn. Blackwell Scientific Publications, Oxford.
- SOOTHILL, J.F. (1967) Chemotherapy in the immunity deficiency syndrome. *Postgrad. med. J.* **43**, Suppl. p. 64.
- SQUIRE, J.R. (1962) Hypogammaglobulinaemia. *Proc. roy. Soc. Med.* **55**, 393.

Abnormalities of spleen and pancreas in trisomy D syndrome

G. P. CLEIN*
M.A., M.B., M.R.C.P.

M. J. MITCHINSON
M.A., M.B., M.C.Path.

Departments of Medicine and Pathology, Cambridge University

NUMEROUS abnormalities have been described in association with trisomy D (Patau *et al.*, 1960; Smith *et al.*, 1963) and include malformations of the brain, eyes, maxilla, heart and great vessels, and genito-urinary tract. Capillary haemangiomas and polydactyly complete what is now a fairly easily recognizable clinical syndrome. The regular association of these malformations with trisomy D is obviously of great significance in morphogenesis and clues to the role of the extra D chromosome must come initially from careful documentation of cases. For this reason we are describing an infant with trisomy D syndrome to emphasize a further morphological feature—namely combined abnormalities of the spleen and pancreas.

Case report

Female infant; 38 weeks; normal delivery. Mother's age, 26 years; father's age, 27 years. Pregnancy was normal throughout. Findings at birth were: cleft palate with hare-lip, microphthalmia with colobomata, micrognathia and low-set ears. The infant was cyanosed and a loud systolic murmur was heard. There were extra vestigial digits on both hands and cutaneous capillary haemangiomas. The infant had a number of convulsions and apnoeic attacks and died after 3 days. The clinical diagnosis was trisomy D syndrome.

Cytogenetics

Cytogenetic studies were performed according to the technique of Moorehead *et al.* (1960) on heart blood taken shortly after death. A total of

FIG. 1. Karyotype of present case.

forty cells was analysed. All showed forty-seven chromosomes, 45-XX-trisomy D (Fig. 1).

Necropsy (P66.156)

Apart from the external abnormalities previously described other congenital malformations found were:

(1) Heart and great vessels. A left superior vena cava received the left jugular and subclavian veins and a left azygos vein, and drained directly

* Present address: Royal Victoria Infirmary, Newcastle upon Tyne, 1.