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Short reports

Coagulation defect of congenital tyrosinaemia

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SUMMARY Three infants with hereditary tyrosinaemia had a severe coagulation defect due to a combination of deficient hepatic synthesis of clotting factors and a consumption coagulopathy. In all three plasma failed to clot normally with the venom of Bothrops atrox (Reptilase) and we attribute this to a defect of fibrinogen (dysfibrinogenaemia). Treatment was unsuccessful, and all died.

Hereditary tyrosinaemia may present in infancy as a severe hepatorenal disorder, with gross abdominal distension, ascites, and hepatosplenomegaly. These features are well recognised.[1] A further major problem may be a profound haemorrhagic disorder; but there are no detailed studies of the coagulation defect.

In recent years it has been recognised that in severe liver disease of adults, particularly hepatoma, not only is there impaired synthesis of the liver and vitamin K-dependent coagulation factors but also defective synthesis of fibrinogen, so called dysfibrinogenaemia. We describe the association of a severe coagulation defect with dysfibrinogenaemia in three infants with hereditary tyrosinaemia.

Methods

Routine coagulation tests were performed as described by Austen and Rhymes.[2] The coagulation factor assay substrates were supplied by Boehringer with the exception of the factor VII assay, for which we used a factor VII deficient beagle plasma, kindly supplied by Dr L Poller.[3] The venom of Bothrops atrox (Reptilase) was obtained from Paines and Byrne, and the Reptilase time was performed by clotting 0·3 ml of plasma with 0·1 ml of Reptilase reagent.

Our normal ranges for plasma tyrosine and methionine are 0·04 to 0·08 mmol/l and 0·01 to 0·38 mmol/l respectively.

Case reports

Case 1. This child was the third child of healthy, unrelated parents. A paternal cousin had died with chronic granulomatous disease. A high blood tyrosine concentration was first noted at a routine screening test at 10 days of age, and responded to vitamin C treatment for a month. Tyrosine was then normal but the methionine concentration was high. The child was well but at 10 weeks he developed abdominal distension and bruising, and umbilical and inguinal herniae. A retroperitoneal haemorrhage was suspected. There was no response to fresh frozen plasma, blood transfusion, and antibiotics. Hepatosplenomegaly and ascites persisted for the next month, with persistence of abnormal coagulation tests. He was transferred to this hospital where he was found to have high plasma tyrosine (1·31 mmol/l) and methionine (2·5 mmol/l) concentrations. Chronic granulomatous disease was excluded with a normal nitroblue tetrazolium test. Treatment was started with a low tyrosine, methionine, and phenylalanine diet; frusemide; and spironolactone. There was no response and he died six days later. The coagulation results are shown in the Table.

Case 2. This baby was the only child of Pakistani parents who are first cousins. Anaemia, hepatosplenomegaly, and gross ascites were detected at the age of 3 weeks. Her haemoglobin concentration was 6·4 g/dl. She was transferred to this hospital as a possible case of tyrosinaemia. Her plasma methionine concentration was 0·965 mmol/l and tyrosine was 0·662 mmol/l. Urine showed a gross generalised aminoaciduria with an appreciable increase in p-hydroxyphenylactic acid and p-hydroxyphenylacetic acid. The serum alkaline phosphatase concentration was very high (1470 K-A U/100 ml), shown by isoenzyme electrophoresis to be of bone origin. In spite of treatment with a diet low in phenylalanine, tyrosine, and methionine which reduced the concentrations of phenylalanine and tyrosine to about 0·1 mmol/l, the baby remained very ill and died at the age of 2 months. No necropsy was performed. Results of the coagulation tests are shown in the Table.

Case 3. This girl was the fourth child of healthy unrelated parents. An older sister had died at the

Table *Results of haematological tests in patients with tyrosinaemia*

Case No	*Date*	*Haemoglobin (g/dl)*	*Platelets ($\times 10^9$/l)*	*Red blood cell fragmentation*	*Prothrombin time (sec)*	*Partial thromboplastin time with kaolin (sec)*	*Thrombin time (sec)*	*Reptilase time (sec)*	*Fibrinogen (g/l)*	*Fibrin degradation products (μg/ml)*	*Coagulation factor assays (% normal adult level)*						*Treatment*
											II	*V*	*VII*	*VIIIC*	*IX*	*X*	
1	25.4.74	9·4	61	+	87	180+	28	180+		10–40				80+			Vitamin K, 1 mg alternate days
	29.4.74	8·5	111	++	15	180	19	82	0·44				16	80			
2	14.9.76	9·3	100	SI	55	102	15·5	80	0·37	<8	15	15	7	100	8	30	Vitamin K, 1 mg intramuscularly, 5 mg orally alternate days
	16.9.76				48	66	23·5		1·32								
3	23.12.80	12·4	85								1	25	1	150	1	4	Fresh frozen plasma vitamin K, 1 mg
	27.12.80				97	92	36										
	29.12.80	9·5		few	96	92	36	150+	0·35	4–8	2	3	1	130	8	4	Factor VIII RA 180%: fresh frozen plasma, 150 ml; vitamin K, 2 mg
	2.1.81				60	103	25										
	6.1.81	6·8	12	+	89	85	18		0·8		6	4	1	145	7	3	
Normal ranges			150–300		12–14	40–45	13–18	15–20	2·0–4·0				50–150				

SI=slight.

age of 5 weeks with a bleeding disease and abdominal distension, later recognised by Dr H B Marsden, who reviewed the necropsy slides, as hereditary tyrosinaemia. No detailed coagulation data were available. Our patient's birthweight was 3 kg. She was breast fed for three weeks and seemed to progress satisfactorily in spite of some puffiness of the face and an enlarging umbilical hernia. At the age of 13 weeks she was referred to this hospital with abdominal distension and ascites, generalised oedema, low grade pyrexia, and cough. Initial tests showed haemoglobin concentration 12·4 g/dl, platelets 85×10^9/l, albumin 17 g/l, alkaline phosphatase 1160 IU/l, calcium 2·22 mmol/l, magnesium 1·01 mmol/l, inorganic phosphate 0·75 mmol/l, bilirubin 35 μmol/l, urea 3·6 mmol/l. Thin layer chromatography of plasma showed increased tyrosine and methionine. Urine chromatography showed gross generalised aminoaciduria with notable excretion of phenolic acids, and galactosuria. Galactosaemia was excluded by finding normal activity of red cell galactose-l-phosphate uridyl transferase. Isoenzyme electrophoresis showed that the high serum alkaline phosphatase concentration was of bone origin, and radiographs showed generalised osteoporosis and early rickets. Blood cultures grew *Klebsiella pneumoniae* and a non-haemolytic streptococcus. Coagulation tests were initially normal. She was first treated with a galactose-free diet, frusemide, ampicillin, and gentamycin. In spite of the treatment her condition deteriorated. On day six coagulation failure was noted and attempts to correct the coagulation defect with vitamin K and fresh frozen plasma were unsuccessful. She became hypophosphataemic and anaemic, and died 14 days after hospital admission. The liver and kidneys at necropsy by Dr M Lendon showed atrophic liver, hypertrophy of the pancreas and the islets of Langerhans, changes characteristic of hereditary tyrosinaemia, and renal tubular necrosis. Coagulation data are given in the Table.

Discussion

It is now evident that the lower concentrations of the coagulation factors seen in normal babies are not solely due to vitamin K deficiency. The concentrations of several coagulation factors are lower than in adults[4] and Künzer[5] has also proposed the existence of a fetal form of fibrinogen. The immaturity of their immune system predisposes to infection and septicaemia with disseminated intravascular coagulation and thrombocytopenia. The combination of these features in babies predisposes to coagulation disorders.

The coagulation factors are synthesised in the

liver, with the exception of factor VIII which is produced by endothelium. In the presence of severe liver disease there is a failure to synthesise the clotting factors, leading to progressive failure of coagulation, with low concentrations of all the clotting factors except factor VIII. These findings were present in our patients and suggest that defective hepatic synthesis, due to the liver failure of tyrosinaemia, contributed largely to the clotting defect.

Reptilase clots fibrinogen by splitting off fibrinopeptide A, in contrast to thrombin which splits off fibrinopeptides A and B. With normal plasma, the thrombin and Reptilase times are similar. Heparin prolongs the thrombin time but leaves the Reptilase time only slightly affected. When the fibrinogen molecule is abnormal, however, that is in dysfibrinogenaemia, the clotting time with Reptilase is proportionately far longer than the clotting time with thrombin.[6] The Reptilase time has been used as a screening test for abnormal fibrinogen in liver disease.[7 8] All three babies showed a Reptilase time much longer than the thrombin time, and on this evidence had dysfibrinogenaemia. They also had anaemia, thrombocytopenia, and hypofibrinogenaemia. Blood films showed red cell fragmentation and in case 1 there was an increase of fibrinogen degradation products. These findings are evidence that a consumption coagulopathy was also contributing to coagulation failure.

Case 3 developed septicaemia which is a recognised cause of disseminated intravascular coagulation and defibrination in babies[4] but we did not observe septicaemia in cases 1 and 2. These findings cannot, therefore, all be attributed to infection. It seems reasonable to conclude that the haemorrhagic defect in the acute form of hereditary tyrosinaemia is the result of hepatic disease. The indicated treatment would seem to be replacement with fresh plasma, blood, platelets, and fibrinogen. In case 3, however, this treatment failed to reverse the defect, probably because of persisting defibrination to which the septicaemia may have contributed. It seems unlikely that the coagulation defect will be treatable without curing the primary hepatic defect.

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Postnatal breast development of preterm infants

An index of gonadal function

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SUMMARY Development of breast nodules after birth was examined in 17 preterm infants; nodules developed regularly in girls but not boys. It is concluded that the pituitary-gonadal axis of preterm infants is active in the months after birth and that in preterm infants there is a definite phase of breast growth in early postnatal life.

In recent years there has been much interest in the development of gonadal function in early life. In boys there is evidence for a surge of testicular androgen secretion after birth, with a peak at about 8 weeks of age.[1] In those born preterm this postnatal testosterone secretion may be even greater.[2] It is not known what contribution, if any, the fetal ovary makes to oestrogen production during pregnancy but during the first postnatal weeks oestrogen