CONGENITAL THYROTOXICOSIS, HEPATOSPLENOMEGALY AND JAUNDICE IN TWO INFANTS OF EXOPHTHALMIC MOTHERS

BY

M. O. SKELTON and B. GANS

From the Group Laboratory and the Paediatric Department, Lewisham Hospital, London

(RECEIVED FOR PUBLICATION MAY 3, 1955)

This paper describes two infants with congenital enlargement of the thyroid and hepatosplenomegaly. One infant died at birth from obstetrical causes, the other lived for 33 days, during which time he was thyrotoxic and jaundiced. Though the first infant was not jaundiced, and, naturally, showed no signs of thyrotoxicosis, we consider that he showed all the other features of the syndrome.

Maternal History

Both infants were the offspring of mothers who had undergone thyroidectomy for Graves's disease, two years and four years respectively, before the birth of the affected infant. In both mothers the course of the thyrotoxicosis was unusual in that there was no weight loss during the course of the disease and the exophthalmos persisted unchanged after operation. We consider that both women had a supra-thyroid (pituitary) type of thyrotoxicosis, and that the anterior pituitary continued to be overactive after the operation. The mother of the first infant was treated pre-operatively with Lugol's iodine and phenobarbitone. The mother of the second infant received Lugol's iodine and thiouracil before her operation. Neither of these women was thyrotoxic during her pregnancy, though the exophthalmos was marked. Their ages were 21 and 25 respectively at the time of delivery. The mother of the first infant was thought, two months after delivery, to show some very minor signs of thyrotoxicosis. At that time her basal metabolic rate was +31%. There was a fine tremor and some tachycardia, but her exophthalmos was out of proportion to the toxic signs and she had lost no weight. The mother of the second infant was not thyrotoxic during or after her pregnancy, and gave birth to a normal living female infant 16 months later. There was no evidence of syphilis, toxoplasmosis or blood group incompatibility in either of the mothers or the infants. The 24-hour 17-ketosteroid excretion in the first mother was estimated two months after delivery, and was 8.65 mg. %.

Infants' History

The birth weight of the first infant was 3 lb. 15 oz. He was born by spontaneous vertex delivery, and his

immediate post-natal condition was good. On the third day his weight had dropped to 3 lb. 5 oz. Throughout the first week he was abnormally active and restless, and appeared ravenously hungry. He became slightly dehydrated and moderately jaundiced at the end of the first week. At that time phenobarbitone, grains $\frac{3}{4}$ daily, only just controlled his hyperactivity, but did not prevent his taking 3 oz. of expressed breast milk every three hours. On the eleventh day (Fig. 1) he was very

FIG. 1.—The thyrotoxic infant on the eleventh day.

emaciated and his jaundice was more marked. The skin was moist, the urine dark, and the stools were pale. There was a suggestion of a stare and exophthalmos. The thyroid was visibly enlarged, the liver reached three fingerbreadths, and the spleen two fingerbreadths, below

the costal margins. There was a regular tachycardia of 170 per minute.

From the 11th to the 33rd day of life the infant continued to be overactive and very hungry, taking avidly from the breast. Continuous sedation was necessary. In spite of an unlimited supply of milk he did not regain his birth weight. The jaundice and exophthalmos fluctuated slightly, but did not disappear. The hepatosplenomegaly and the enlargement of the thyroid persisted unchanged. After the third week of life his pulse declined from 170 to 140, but did not drop below this figure. On the 33rd day of life his temperature, which had been normal throughout, rose to 105° F., and he was found to have a bronchopneumonia, to which he succumbed after 24 hours in spite of treatment.

Laboratory investigations gave the following results:

The direct Coombs test was negative, and the indirect van den Bergh gave 1·2 mg. at eight days, 4 mg. at 19 days.

Radiographs of the chest and a skeletal survey were normal.

A blood count at 11 days gave: 129% Hb, 9,000 W.B.C. (52 polymorphs, 1 eosinophil, 42 lymphocytes, 5 monocytes) at 19 days, 149% Hb, 1,500 W.B.C. (33 polymorphs, 3 eosinophils, 46 lymphocytes, 8 monocytes).

In the urine there was a trace of a reducing substance, but no bile salts, no urobilin and a trace of bile pigments, but no cytomegalic inclusion bodies.

There was no excess galactose in the serum. The blood sugar level was 57 mg. %, the blood cholesterol level 144 mg. %. The prothrombin time (Quick's method) was 15 seconds.

The C.S.F. contained 25 mg. protein, 46 mg. sugar, 1 lymphocyte, 7 red blood cells.

In the stools there was trypsin but no urobilin.

The second infant was born after a labour lasting 39 hours and 25 minutes. His birth weight was 4 lb. 7 oz. He was shocked and asphyxiated, and though the heart continued to beat for 15 minutes, he died without having breathed, in spite of intubation and phrenic nerve stimulation. He was not icteric.

Morbid Anatomy

Case 1. Necropsy was performed 48 hours after death.

The body is that of a male infant weighing 1·6 kg. There is moderate jaundice of the skin and sclerotics. The body appears wasted and dehydrated and the skin wrinkled, and there is no buccal pad of fat. The neck appears fuller than normal.

The thyroid (weight 4·6 g.) is uniformly enlarged (Fig. 2); the lateral lobes measure 3 cm. in length, 1·4 cm. in width at the lower poles and 1·1 cm. anteroposteriorly. The thyroid is pale brown and normal in consistency and no colloid is visible on the cut surface. Microscopically there is a definite slight increase in fibrous tissue with thickening of the connective tissue septa. This divides the thyroid tissue into a number of small lobules each consisting of groups of small acini which are packed together, the walls lined by hyper-

plastic epithelium. The acini contain no colloid and consequently appear as small nodular aggregates of cells. The epithelial cells have relatively scanty cytoplasm and the nuclei are rather large and dark staining. Many cells are binucleated. There are no lymphorrhages. There is no congestion of the gland (Fig. 3).

The thymus (12 g.) appears normal macroscopically and microscopically.

FIG. 2.—The enlarged thyroid of the first infant.

The liver (112 g.) is enlarged uniformly and dark brownish green. Its shape is normal and on section the parenchyma feels firmer and more resistant than normal. There is no gross evidence of cirrhosis. Microscopically there is an early cirrhosis; in the portal areas there is fibrosis and proliferation of bile ducts. From these areas a fine fibrosis radiates out between the columns of liver cells, and an early multilobular cirrhosis is developing. The fibrosis also extends between the liver cells, breaking them up into short columns (Fig. 4). There are a few foci of haemopoiesis in the sinusoids and portal areas. The liver cells are rather small and contain brown pigment granules, apparently bile, and the bile canaliculi contain plugs of dark green bile. Occasional large multinucleated hepatic cells are seen. The Kupfer cells are swollen and contain pigment granules. A few hepatic cells contain a fine powdering of iron pigment.

FIG. 3.—Thyroid showing marked cellularity. Acini not distinguishable, no colloid present. (Haematoxylin and eosin $\times 270$.)

FIG. 4.—Liver showing early cirrhosis with fibrosis starting around portal areas and radiating out therefrom. (Haematoxylin and eosin $\times 65$.)

The gall bladder and extrahepatic bile ducts are patent. The spleen (weight 9 g.) is enlarged, and on section shows a moderate degree of congestion.

The lungs show a bronchopneumonia.

The retrobulbar tissues show no abnormality.

All other tissues and viscera appear macroscopically and microscopically normal.

Case 2. The body is that of a premature male infant weighing 2.00 kg. There are numerous petechiae in the skin of the trunk and limbs, but no evidence of injury. The neck appears abnormally full, the veins of the neck are congested and the face cyanosed. There is no jaundice or generalized oedema, but the conjunctivae are oedematous and show a few minute haemorrhages.

The thyroid (8 g.) has a volume of 9 ml. Both lateral lobes and the isthmus are symmetrically and uniformly enlarged. The lateral lobes are 3 cm. long, 2 cm. wide at the lower poles and 1.5 cm. antero-posteriorly. On gross section the parenchyma is dark red, of a homogeneous appearance and shows no colloid on the cut surface. The enlarged thyroid closely embraces the trachea but does not appear to have caused any mechanical obstruction. Microscopically the thyroid

tissue is considerably autolysed and the veins and capillaries are congested. The acini are small and closely packed, the epithelial cells are of cuboidal type, in some places several cells thick on the basement membrane. Most of the small acini show small clumps of desquamated epithelial cells in the lumina. There are numerous irregularly shaped haematoxylin staining masses composed of three or more fused nuclei. There is no colloid or lymphoid tissue.

The thymus (23 g.) is enlarged, an appearance which, on microscopic examination, is seen to be due to congestion only.

The liver (150 g.) is uniformly enlarged but of normal shape. The parenchyma on gross section is normal in colour but congested. Microscopically the hepatic veins and sinusoids are congested. There is a considerable amount of haemopoietic tissue in the sinusoids and portal areas. The parenchyma cells are somewhat autolysed and many show intracellular masses of bile pigment. There are small collections of bile pigment in the canaliculi. The Kupfer cells are swollen and contain bile pigment. No iron is present. There is early proliferation of bile ducts in some of the portal areas and a very early proliferation of reticulum fibres round the

portal areas and between the liver cells, indicating an early diffuse fibrosis.

The gall bladder contains bile and the bile ducts are patent.

The spleen (24 g.) is uniformly enlarged. Microscopically this enlargement is due to intense congestion.

The heart shows a few subepicardial petechiae.

The lungs show a few similar petechiae beneath the pleura and are not expanded.

Examination of all other viscera shows no significant change macroscopically or microscopically.

The thyroids of both these children show a picture of hyperplasia of the epithelium. This is particularly marked in Case 1, with no colloid formation.

The appearances of the liver in Case 1 are those of an early diffuse hepatic fibrosis. The process is beginning in the portal areas and extending from thence towards the centres of the lobules, and is also extending between liver cells. The bile plugs in the canaliculi suggest an obstructive element that is probably secondary to the fibrosis, and there is no obstruction of the extrahepatic bile channels. The liver in Case 2 shows a very early stage of this process of fibrosis.

The enlargement of the spleen is congestive in nature and probably indicative of a slight portal hypertension in Case 1, secondary to the hepatic fibrosis. In Case 2 it is probably a further expression of the generalized congestion of all viscera which is much more marked in Case 2 than Case 1.

Discussion

Jirsová and Brychnáč (1953) described an infant who appeared in almost all respects identical with our two cases. His mother had persistent exophthalmos after a partial thyroidectomy. Two years after operation she gave birth to a child whose birth weight was 2,106 g. and dropped to 1,930 g. after two days. The baby was overactive and ravenous, and his muscle tone was increased. He had exophthalmos, a stare and a persistent tachycardia of 180. The sclerae were icteric and the stools were clay coloured. The thyroid was visibly enlarged, and the liver and spleen were enlarged 2 cm. and 3 cm. respectively below the costal margins. He made a spontaneous recovery, and at the age of 3 months his exophthalmos was barely noticeable, his pulse was 120, his weight was 4,300 g., and the goitre, jaundice and hepatosplenomegaly had disappeared.

We have been unable to find any other cases of this kind in the literature. It would appear that our two infants, and the infant described by Jirsová, differ materially from the three cases of congenital thyrotoxicosis which have been recorded. White's case (1912) was the offspring of a mother who developed thyrotoxicosis—not treated by operation—when she was five months pregnant. The child weighed 4 lb. 6 oz. at birth, had a tachy-

cardia of 200, exophthalmos, tremor of the hands and a uniform enlargement of the thyroid. He died 36 hours after birth, probably from a cerebral birth injury. Margetts' infant (1950) was reported by his mother to have been lethargic and difficult over his feeds at first. His birth weight was 5 lb. 13 oz. When first seen at the age of 4 weeks he was thin and restless, blinked infrequently, and the palpebral fissures were widened. He had a tachycardia of 160 to 200. However, the thyroid was not palpable. At the age of 3 months the exophthalmos and hyperkinesis had diminished and his pulse was 135 to 160. His mother had been thyrotoxic for one year before delivery. Her disease had worsened during pregnancy and had been treated with phenobarbitone and digitalis. Fischer (1951) reported an infant whose mother developed thyrotoxicosis during the last trimester of her pregnancy and had been treated with propylthiouracil and sedatives. The baby weighed 7 lb. at birth and was restless and difficult to feed during the first week of life. He was pyrexial, dehydrated and slightly cyanosed, and had a tachycardia. Fullness of the neck, hoarseness, tremor, moist skin and exophthalmos became apparent during the second week. The cyanosis, pyrexia and dehydration did not disappear until the child was 4 weeks old, in spite of oxygen, penicillin and subcutaneous fluid therapy. Lugol's iodine, given at 3 weeks, had no effect on the signs of thyrotoxicosis. These slowly subsided between the fourth and tenth weeks, at which time the neck was still full and slight exophthalmos was still noticeable.

Neither jaundice nor hepatosplenomegaly was a feature of any of these cases of congenital thyrotoxicosis. The thyrotoxicosis was evidently the result of an excess of maternal thyrotropic hormone reaching the foetus via the placenta. This would explain the transient nature of the disease in the infants who survived. No doubt the thyrotoxicosis in our and Jirsová's cases was due to a similar mechanism.

It is interesting that all the reported cases of congenital thyrotoxicosis have occurred in male infants. The usual sex incidence of the disease in children is given by Kennedy (1950) as five females to one male. Possibly the female foetus is better equipped to neutralize in some way her mother's excess thyroid-stimulating hormone. It will be noted that the mother of our second infant subsequently gave birth to a normal female child though her pituitary was then still producing excessive amounts of thyroid-stimulating hormone.

We can only speculate as to the cause of the jaundice and the enlargement of the liver and spleen in which our and Jirsová's cases differ from those of

White, Margetts and Fischer. The mothers of the former infants had all undergone thyroidectomy at varying periods before delivery, and had continued to show signs of thyrotoxic hormone excess during and after the birth of their infants. We feel that this continued excess of thyrotropic hormone may be responsible for the hepatosplenomegaly and jaundice which complicated the congenital thyrotoxicosis in Jirsová's and our cases. On the basis of the six infants described, it would appear that women who continue to produce an excess of thyroid-stimulating hormone after their thyroxin output has been reduced to normal by thyroidectomy can give birth to infants with congenital thyrotoxicosis, hepatosplenomegaly and jaundice. The offspring of women not operated on for their thyrotoxicosis may show an uncomplicated congenital thyrotoxicosis. No help can be gained in this problem from animal experiments, as nothing appears to be known of the effect on the foetus and neonate of maternal, pituitary, thyrotropic hormone excess.

The hepatosplenomegaly and jaundice may have been due to thyrotoxic liver damage, an established complication of thyrotoxicosis in adults. However, it seems improbable that such damage could have occurred in such a short time, or that it could have

occurred *in utero*, as one would have to postulate in our second case.

Lastly, a neonatal hepatitis complicating the congenital thyrotoxicosis must be considered as a cause of the jaundice and hepatosplenomegaly. Neither the clinical picture nor the histological findings in the liver support such a diagnosis, and neither of the infants' mothers had suffered from infectious hepatitis.

Summary

A clinical and pathological account is given of two infants with a syndrome of congenital thyrotoxicosis, jaundice and splenomegaly. Their mothers had been operated on for thyrotoxicosis, and had continued to show signs of thyrotropic hormone excess after operation, during pregnancy and after delivery. It is suggested that this excess of thyrotropic hormone may account for the disease picture found in the infants.

REFERENCES

- Fischer, P. M. S. (1951). *S. Afr. med. J.*, 25, 217.
 Jirsová, V. and Brychnáč, V. (1953). *Pediat. Listy*, 8, 107.
 Kennedy, R. L. J. (1950). In Brennemann's *Practice of Pediatrics*, vol. 1, ch. 38, p. 13. Hagerstown, Maryland.
 Margetts, B. M. (1950). *Proc. roy. Soc. Med.*, 43, 615.
 White, C. (1912). *Ibid.*, 5 (Obstet. Sect.), 247.