LEPRECHAUNISM

BY

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'Are you going to listen to what I am telling you about the Leprecaun?' said the Thin Woman in James Stephens's *The Crock of Gold*. 'I am not', said the Philosopher, and the description by Donohue (1948) of a case of 'dysendocrinism' seems to have received as little notice. Now he and Uchida (1954) have redescribed the patient and given an account of her sister (who was similarly affected) under the title of 'Leprechaunism'.

Their patients were daughters of consanguineous parents. The children's growth appeared to be halted at about the seventh month of pregnancy; the elfin facies suggested the name; both children died and at necropsy showed evidence of endocrine disturbance in the ovaries, pancreas, breasts and clitoris, as well as deposition of glycogen and iron in the liver and calcium in the kidneys.

When the description of the Toronto cases appeared, two children were seen in London who had some of the same characteristics. In one, an older child, large ears and congenital mammary hypertrophy suggested the diagnosis; in the other, the general resemblance of the baby to that illustrated in Donohue and Uchida's Fig. 1 operated similarly. In neither case was the identity complete, for in each some of the abnormalities of the Canadian infants were lacking.

Case Reports

Case 1. This girl was the third child of healthy Jewish parents not related by blood; the elder sister and brother were also well. Pregnancy and delivery were normal; the birth weight was 6½ lb. The baby was always difficult to feed, for she would not suck for long, although she did not appear tired. Breast feeding was abandoned at the end of the first week, but bottle feeding was no better. At the age of 12 weeks she weighed only 7½ lb., so she was admitted to the Victoria Hospital, Blackpool, under Dr. Gordon Hesling. Detailed investigations showed no reason for her failure to thrive and even when alternate feeds were given by oesophageal tube she did not gain weight. At 16 weeks Dr. Hesling referred her to Dr. Reginald Lightwood who admitted her to The Hospital for Sick Children, Great Ormond Street, London.

She was seen to be (Fig. 1) a small, thin, fretful baby who cried lustily. Her cheeks were sunken, chin pointed, eyes wide apart and showing very dark irides, nose negroid and ears set low on the head (Fig. 2). The head measured 15¼ inches in circumference, the anterior fontanelle was wide, the posterior fontanelle was closed. The hands and feet were large, and the skin creases showed brown pigmentation. The nipples and areolae were large and protuberant; the clitoris was enlarged (Fig. 3). Moro and grasp reflexes were present. There was a rough systolic praecordial murmur; the blood pressure was 95/65 mm. Hg.

Various diagnoses had been considered and found to

FIG. 1.—Case 1: Emaciation and prominence of nipples (age 4 months).

FIG. 2.—Case 1: High forehead, wasting of face, wide eyes, pointed chin, low ears (age 4 months).

be untenable when the paper by Donohue and Uchida (1954) appeared and the resemblance between our patient and theirs was noticed; the hyperplasia of nipples and clitoris reinforced the impression that this infant might be an example of leprechaunism.

Between the ages of 3 and 8 months results of the following investigations were normal: blood values for urea, calcium, sodium, potassium, bicarbonate (all done twice); chloride, galactose, Wassermann reaction, toxoplasma, complement-fixation and Sabin-Feldman dye tests, and amino-acids; urinary amino-acids (twice) and sugars by chromatography, blood counts and sedimentation rate, leucocyte sex chromatin, tryptic activity of faeces (twice), serum antithrombin titre, electrocardiogram, radiographs of chest, heart and oesophagus (barium swallow).

The urine occasionally contained a trace of albumin, but was otherwise normal (no phenylpyruvic acid); the total plasma proteins were 5.7 g. % with some increase in α_2 , β and γ globulins.

The growth failure was associated with a decrease in bone development: the bone age at 4 months was up to the standard of girls of 1½ months, and at 8 months it had reached the standard for 3 months. Pituitary hypofunction was suspected as the cause. Radiography of the skull showed a normal pituitary fossa; air encephalography revealed normal third and fourth ventricles, a normal aqueduct, but some evidence of atrophy of the right cerebral hemisphere as the right lateral ventricle

was larger than the left, and there was possibly some widening of the sulci over this hemisphere. Cerebrospinal fluid was examined twice and was normal except that on one occasion the sugar content was low, 34 mg. %. Similarly, the fasting blood sugar was occasionally rather low; on different occasions the figures were 110, 70, 78, 55, 62 and 56 mg. %; by paper chromatography the blood glucose was estimated to be 37 ± 2 mg. %. Blood glycogen was normal or low, 6.8 mg. %. A glucose tolerance test was normal, and so were the glucose and the eosinophil responses to the injection of adrenalin, but the response to insulin was abnormal, showing an excessive, and more especially a prolonged, fall in blood sugar.

The urinary excretion of follicle-stimulating hormone was less than 5 mouse units in 24 hours, i.e., not excessive; a vaginal smear showed no evidence of oestrinization, the excretion of 17-ketosteroids was 0.6 mg. and 0.43 mg./24 hours (normally not over 0.1 mg., Talbot, Butler, Berman, Rodriguez and MacLachlan, 1943). Laparotomy showed that the liver and spleen were slightly enlarged and the ovaries were cystic, but no microscopic abnormality was found in small biopsy specimens of liver, ovary or pancreas.

The infant was kept in hospital from the age of 4 months to 9 months. During this time she made slow progress. The head increased in circumference by 1½ in. (16½ in. at 9 months), weight increased from 8½ lb. to 10½ lb., length from 22½ in. to 23½ in. The cardiac murmur became almost inaudible. Cortisone (14 g. by mouth in one month) appeared not to affect her progress. On discharge at 9 months she seemed to have reached

FIG. 3.—Case 1: Wasting, enlargement of clitoris (age 4 months).

a 5-month level in some motor activities, but she had very little control of her back, although head control was good.

This child resembled the patients of Donohue and Uchida in external appearance, enlargement of nipples, areolae and clitoris, defective growth, and cystic changes in the ovaries. By contrast the ears were not particularly large, pregnancy and weight at birth were normal, there was no facial hirsuties, and no histological changes were found in liver or pancreas. The slow growth, delayed ossification and hypersensitivity to insulin suggested that there was a deficient production of growth hormone by the pituitary.

Case 2. This girl was referred to Guy's Hospital when she was 2½ years old. I thought she was simply mentally retarded and noted the associated congenital anomalies of enlargement of the ears and mammae. Two days later I read Donohue and Uchida's account of leprechaunism, and then arranged for her to be admitted to hospital for investigation.

She was the third child of healthy parents who were not related by blood; her two older and one younger brothers were well. Pregnancy and birth were normal, when she weighed 7 lb. She was easy to feed and enjoyed good health except for eczema, which started at 9 months and was not severe. She developed slowly; sat at 1 year, stood at 1½ years and walked alone at 2½ years. She fed herself with her hands but could not use a spoon and used only two words with meaning. She was thin, weighing 26 lb. (average for 2 years), height 36 in. (average for her age), head circumference 18 in. (average for 1 year), span 36½ in. (average for 3½ years). She was a blue-eyed, fair-haired child, with a vapid expression and rather wide eyes, but her facies did not much resemble that of the

FIG. 5.—Case 2: Prominence of mammary areola (age 2½ years).

leprechaun babies. The ears were large and rather bat-like (Fig. 4). Mammary enlargement had been noticed at birth, but was thought to be diminishing gradually. The areola was chiefly involved (Fig. 5) and the tissue under it felt like mammary tissue, not fat. The clitoris was not enlarged. There was slight contracture which prevented either ring finger from being fully extended; the second toe on the left foot was permanently slightly dorsiflexed; there was a dimple over the sacrococcygeal junction, slightly to the right side.

The liver was palpable two fingerbreadths below the costal margin. The blood pressure was 95/65 mm. Hg. She was slightly anaemic: Hb 66% (10.2 g. %), white blood count normal; the blood calcium, phosphate, alkaline phosphatase, sodium, potassium, chloride and protein (albumin and total globulin) were normal. The blood urea was 41 mg., plasma bicarbonate 34.7 vol., and blood glycogen 13.4 mg. % (normal). Urinary gonadotrophins were not increased (negative to 12 mouse units in a 24-hour specimen), but 17-ketosteroids were slightly raised: 3 mg. and 2.4 mg. in 24-hour specimens (normally not over 0.4 mg. according to Talbot *et al.*, 1943). A vaginal smear showed a few squames with slight reddish staining indicating the presence of glycogen. Radiographs of the whole skeleton showed no abnormality except a bone age of 1-1½ years; air encephalography showed (as in Case 1) some dilatation of the right lateral ventricle. The glucose tolerance curve was rather high; injection of adrenalin also was followed by

FIG. 4.—Case 2: Wide eyes, large ears (age 2½ years).

a considerable rise of blood sugar from 62 to 134 mg. % in 45 minutes. The injection of insulin was followed (as in Case 1) by an unusually prolonged fall in blood sugar.

Laparotomy showed slight enlargement of the liver; the spleen was about twice the normal size, the ovaries were enlarged and cystic measuring on the right side $1\frac{1}{2} \times \frac{3}{4} \times \frac{1}{2}$ in. The kidneys and pancreas appeared normal. The biopsy specimen of the pancreas was normal; in the liver there was no increase in iron but there was moderate diffuse glycogen infiltration, predominantly centrilobular, and chemical assay showed 1.58 g. % (normal 0.4%).

Methyltestosterone, 5 mg. in propylene glycol, was given daily by mouth for eight weeks. During this time weight increased by only 2 lb. and height perhaps not at all (it was difficult to measure accurately), but the mammary enlargement seemed a little less. The bones and epiphyses in the limbs had increased in size, but there were no new carpal centres. There was no significant change in excretion of urinary gonadotropins or 17-ketosteroids (2 mg./24 hr.); blood urea was normal (29 mg. %); a vaginal smear showed faint staining for glycogen; after insulin injection there was still some delay in restitution of the blood sugar level, but the fall was not as great as before. One month later (after no further testosterone had been given) the weight had increased by 2½ lb. and the nodular feeling of the mammary tissue was no longer detectable.

This child resembled the cases of Donohue and Uchida in having large ears, congenital mammary enlargement, increased liver glycogen, large cystic ovaries and decreased bone age. By contrast, pregnancy, birth weight and feeding were normal and the clitoris was not large. The facial appearance was not characteristic, but she was much older than the other patients. She also had increased response to insulin and slightly increased 17-ketosteroid excretion.

Discussion

For practical purposes it suffices to define a leprechaun as 'In Irish folk-lore, a pigmy sprite' (*Shorter Oxford English Dictionary*). Something more detailed is needed for the definition of leprechaunism, but as yet too few cases have been described to enable one to list the essential and the concomitant features. One cannot even answer the important and perhaps critical question, Are there males with leprechaunism?

Some failure of growth, including delay in ossification; a characteristic facies in infancy, usually with large ears, wide eyes and hollow cheeks; congenital enlargement of mammary ducts, areolae and nipples; enlargement of liver and ovaries, with an unusually great number of follicular cysts in the latter; all these seem to be important features. In addition, the clitoris and labia minora may be large, and so may the kidneys and spleen. Mental defect

is probably one of the major features, but only one of the four patients has been seen at an age when this is certain.

Further study of carbohydrate metabolism is likely to help. In the two babies examined at necropsy, there was hyperplasia of the islets of Langerhans and in one the insulin content of the pancreas was found to be much increased. In three of the four children the liver contained excessive glycogen, but it was (in the two surviving patients) easily mobilized by adrenalin; their reaction to insulin was excessive.

We can imagine that these children resemble those suffering from Turner's syndrome in that they are born with certain anatomical abnormalities—in this case the characteristic facies, large ears and perhaps mental defect—but that some of their other peculiarities are secondary to a developmental anomaly of an endocrine gland. Some of the effects may well be secondary to pituitary deficiency: delay in bone growth, failure to respond to hypoglycaemia induced by insulin, and the wasting seen in the three babies, point in this direction. Pituitary deficiency alone would, however, be unlikely to cause mammary and clitoridean enlargement, or a slight increase in excretion of 17-ketosteroids—rather, the reverse.

In discussing this difficulty with Dr. Douglas Hubble, he suggested that overproduction of oestrogens should be considered. The ovaries were reported to be cystic in all four cases and were certainly enlarged in three. This enlargement might be assumed to occur in foetal life independently of the pituitary and it might be associated with increased production of oestrogens. This would explain the enlargement of nipples, areolae and mammary ducts. The evidence of experiments in animals has been well summarized by Burrows (1949). Oestrogens inhibit the production of pituitary growth hormone in the rat (Reece and Leonard, 1939; Gaarenstroom and Levie, 1939; Griffiths and Young, 1942), increase insulin production by the pancreas (Griffiths and Young, 1940), which is a possible cause of the failure to respond to hyperglycaemia induced by the injection of insulin, and produce hypertrophy of labia minora (Lewis, 1933). The enlargement of the clitoris seen in three cases was not as great as in adrenal hyperplasia and is perhaps analogous to the enlargement which occurs at puberty. Hypercalcaemia was not demonstrated in our patients, but the kidneys were calcified in the Canadian cases, and it is interesting to recall that oestrogen administration has been found to cause a rise in serum calcium in mice (Wentworth, Smith and Gardner, 1940).

This unsure hypothesis may be summarized by suggesting that in leprechaunism there are congenital (probably genetic) abnormalities of the face, ears and ovaries; that the ovaries may produce oestrogen in excess and that this may cause: (1) slight hyperplasia of nipples, areolae, mammary ducts, clitoris and labia minora, with slight increase of 17-ketosteroid excretion (prepubertal changes); (2) decrease of pituitary growth hormone which causes wasting of the soft tissues and delay in the growth of bones, as well as increased insulin production, and lack of response to hypoglycaemia (metabolic disturbances).

This hypothesis indicates the need for assay of oestrogens (which we were unable to carry out) in such cases, and for discovering whether an analogous condition occurs in the male.

Androgens inhibit oestrogens so treatment with male hormones could be tried. As yet nothing impressive has come out of such a trial in these two patients.

Summary

In 1954 Donohue and Uchida described two

sisters with a characteristic facies, large ears, hyperplasia of mammary ducts, clitoris and ovaries, failure to grow, and increased glycogen in the liver and insulin in the pancreas. Two children thought to belong to the same group are described here.

These children, it is suggested, may perhaps combine anomalies of anatomical development with abnormalities caused by ovarian hypersecretion starting in foetal life.

My thanks are due to my colleagues, too numerous to mention individually, who have helped to investigate these patients.

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