Congenital Iodide-induced Goitre with Hypothyroidism

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Iodide-induced goitre with or without hypothyroidism is an unusual complication of prolonged iodide therapy. It has been reported both in children and adults (Bell, 1952; Morgans and Trotter, 1953; Turner and Howard, 1956; Skaggs and Cooke, 1956; Rubinstein and Oliner, 1957; Paley, Sobel, and Yalow, 1958; Paris *et al.*, 1960; Falliers, 1960; Oppenheimer and McPherson, 1961). Congenital goitres have also been reported in the offspring of euthyroid mothers who received iodide therapy for asthma or other illnesses during their pregnancies (Parmelee *et al.*, 1940; Bongiovanni *et al.*, 1956; Petty and DiBenedetto, 1957; Morgans and Trotter, 1959). Though thyroid function studies were not obtained on these reported cases, it is inferred that the babies were euthyroid. In 1962, Martin and Rento described the first two cases of iodide-induced goitre with hypothyroidism in newborn infants, and a similar case was reported by Crougns and Visser in 1965.

We here report 3 additional cases of iodide-induced goitre with hypothyroidism in newborns, and comment on the pathogenesis of this type of thyroid dysfunction.

Case Reports

Case 1. A male infant was first seen aged 18 days, because of swelling in the neck, difficult breathing, and attacks of cyanosis dating from birth. Pregnancy and labour had been normal, but the mother, age 33 years, had been kept on oral tablets containing potassium iodide because of chronic asthma. She had taken 600 mg. potassium iodide daily during the previous 10 years. She had given birth to 7 other children, 4 of them before and 3 during iodide medication. All were living and well, with no history of thyroid enlargement at birth. The mother herself was clinically euthyroid and her thyroid gland was normal in size.

On admission, the baby was mildly cyanotic, with marked inspiratory stridor on crying. The face was slightly puffy and the tongue enlarged and protruded. The skin was pale and mottled. There was conspicuous enlargement of the thyroid gland, which was moderately firm and smooth. Heart, chest, abdomen, and nervous system were clinically normal.

Skeletal x-ray showed delayed bone age, with absence of the epiphysial centres of the lower end of femur, upper end of tibia, and cuboid bone.

Blood Chemistry. (Bioscience Laboratory, California) PBI 12.8 $\mu\text{g.}/100\text{ ml.}$ (adult normal 4-8 $\mu\text{g.}/100\text{ ml.}$), total iodine 35 $\mu\text{g.}/100\text{ ml.}$ (adult normal less than 8 $\text{mg.}/100\text{ ml.}$), thyroxine iodine 1.9 $\mu\text{g.}/100\text{ ml.}$ (adult normal 3.2-6.4 $\mu\text{g.}/100\text{ ml.}$)

Because of the marked enlargement of the thyroid gland and the clinical and laboratory evidence of hypothyroidism, the infant was given desiccated thyroid 30 mg. daily for two weeks, followed by 60 mg. daily for 3 months. At follow-up there was rapid disappearance of the cretinoid manifestations and progressive decrease in the size of the goitre until disappearance at the age of 1 year. The child is now 2½ years, with normal growth and development.

Case 2. A female infant was first seen aged 1 month, having been transferred from the surgical department because of a big thyroid swelling dating from birth. The mother, age 28 years, had bronchial asthma and, from the age of 2 years, had taken 1 g. potassium iodide daily, up to the time of delivery. Except for some exacerbations of the asthma, the pregnancy had been uneventful. She had given birth to 5 other infants who were all in good health; none had had a goitre at birth. On admission, the mother was clinically euthyroid with a normal-sized thyroid gland.

The baby appeared cretinoid, pale, with some puffiness of the face, a large protruded tongue, and some mottling of the skin. The thyroid gland was moderately enlarged, smooth, and firm. Heart, chest, and abdomen were normal. Skeletal x-rays showed absence of the epiphysial centres of the lower end of femur, upper tibia, and cuboid bone. The infant was put on desiccated thyroid 30 mg. daily for two weeks and 60 mg. daily for 2½ months. She gradually lost her cretinoid features. The thyroid diminished gradually in size until it attained the normal size at 9 months.

The infant is now over 1 year and 4 months old and is normal physically and mentally.

Case 3. A female infant, born at term, was seen aged 2 days, because of a large swelling in the neck noticed at birth. The mother, age 23 years, a chronic asthmatic, had been maintained for the last 3 years on a bronchodilator mixture containing a daily dose of 0.9 g. potassium iodide. She was euthyroid with no apparent goitre.

FIG.—Case 3, showing marked enlargement of the thyroid gland.

The baby was well developed, and in no distress. Skin was pale, with some mottling, and the face was slightly puffy. Both lobes and isthmus of the thyroid gland were markedly enlarged and soft (Fig.). Other systems were normal.

Skeletal x-rays showed absent cuboid, upper tibial, and lower femoral epiphyses. The infant was put on desiccated thyroid 30 mg. daily for 2 weeks, then 60 mg. daily. At 3 months she was thriving, though the thyroid gland was still much enlarged.

Discussion

The 3 infants presented had obvious goitres, with pressure symptoms in Case 1. Hypothyroidism was diagnosed from the clinical picture, from the retarded bone development on x-ray, and, in Case 1, from the blood chemistry. Clinically, all 3 cases had the pallor, puffy face, enlarged protruded tongue, and skin mottling of the cretin. Radiologically, there was absence of epiphysal centres normally present at birth. Laboratory studies done in Case 1 showed a thyroxine iodine level of $1.9 \mu\text{g./100 ml.}$, much below the normal. The raised protein-bound iodine was explicable, as iodide (which was raised to 35 mg./100 ml.) is precipitated with protein in the routine determination of PBI (Danowski and Greenman, 1949).

The relation between excessive iodide administration to the mothers before and during pregnancy and the occurrence of goitre with hypothyroidism

in their offspring was clear. Other causes of congenital goitre with hypothyroidism could be easily excluded. In endemic cretinism the mother must be iodine deficient during pregnancy. In familial goitrous cretinism there is usually a positive family history, and the infant is hypothyroid unless supplemented with daily thyroid hormone throughout life.

The pathogenesis of iodide-induced goitre with or without hypothyroidism is still the subject of controversy. Transplacental passage of excessive amounts of iodide appears to depress hormone synthesis by the fetal thyroid gland. Goitrous enlargement results from the consequent increased pituitary thyrotropic secretion (TSH). Precisely how thyroid function is suppressed by excess iodide is, however, not known. Iodide ions in excess apparently interfere with the peroxidase mechanism responsible for the liberation of free active iodine capable of combining with tyrosine (Fawcett and Kirkwood, 1953; Rubinstein and Oliner, 1957; Paley *et al.*, 1958; Paris *et al.*, 1960; Wilkins, 1965). Galton and Pitt-Rivers (1959) found that acute iodide loading in rats induced a striking rise in the ratio of intrathyroidal mono-iodotyrosine to di-iodotyrosine, suggesting that iodide blocks the di-iodinating enzyme more completely than the mono-iodinating one. Furthermore, iodide ion in excess may inhibit the release of thyroxine from the gland (Wilkins, 1965). There is good evidence that iodide also inhibits TSH secretion directly (Greer and DeGroot, 1955) or has a direct action on the thyroid cell which is antagonistic to the action of TSH (Greer and DeGroot, 1956; Solomon, 1956; Werner, Spooner, and Hamilton, 1955; Green and Ingbar, 1962).

Though such mechanisms may explain the occurrence of iodide-induced goitre with or without hypothyroidism, they fail to explain why these occur in the offspring of only a minority of the mothers exposed to large doses of iodides over long periods, since most patients who take iodides over long periods remain euthyroid, and goitre does not develop either in them or in their offspring. The mothers of our three cases were all euthyroid and with no thyroid enlargement in spite of being on large doses of iodides for years. Again, while on this medication they gave birth to other euthyroid and non-goitrous offspring. As an explanation for this finding, it has been suggested that in affected subjects there may be a basic defect in thyroid hormone synthesis (Hydovitz and Rose, 1956), which is intensified by excessive amounts of iodine to the point at which hormone formation ceases. Dimitriadou and Fraser (1961) suggest

that this basic difficulty may be in converting iodine to mono-iodotyrosine. Recent studies by Harrison, Alexander, and Harnden (1963) and Croughs and Visser (1965) showed that in this disorder there is a lack of normal homeostatic control between thyroid and pituitary glands, either at the thyroid or pituitary level. This could lead to the development of goitre and hypothyroidism in the following manner. When the level of iodide in the plasma is raised, the absolute iodine uptake is at first increased, leading to formation and secretion of increased amounts of thyroid hormone. In normal subjects there is a compensatory decrease in the secretion of TSH, resulting in a fall in uptake of iodine by the thyroid. But in affected patients, pituitary or thyroid autonomy maintains iodine uptake at a persistently high level. Eventually, so much iodine accumulates in the thyroid that organic binding is inhibited and synthesis of thyroid hormone is consequently impaired. As the blood level of thyroid hormone falls and hypothyroidism occurs, increasing stimulation of the thyroid by TSH leads to goitre.

It is often said to be unnecessary to treat congenital iodide-induced goitre, whether with or without hypothyroidism. This is based on the assumption that the thyroid gland, once released from the inhibitory effect of excess iodide of the mother, will produce sufficient amounts of thyroxine. It seems, however, that the interval required after birth for the thyroid to produce a sufficient amount of hormone varies. In Case 1, the thyroxine iodine 20 days after birth was $1.9 \mu\text{g./100 ml.}$ which is much below normal, and the baby was then clearly hypothyroid clinically. As a normal level of thyroid hormone is essential for proper mental and physical development in early infancy, we did not hesitate to administer desiccated thyroid to this baby, treatment being continued for 3 months to cover this critical period. The same policy was accepted for our other 2 cases. Administration of thyroid hormone to these newborns also may speed the reduction in size of the goitre, and hence be of value when there are obstructive symptoms.

Summary

Three cases of congenital iodide-induced goitre with hypothyroidism are reported. The mothers who were euthyroid and with normal-sized thyroid glands had received large doses of iodides orally for years. The sites of block of thyroid hormone formation due to excess iodides are discussed.

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