SPORADIC GOITER DUE TO HYPOTHYROXINOGENESIS. REPORT OF FOUR CASES WITH IODINE ORGANIFICATION DEFECT

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by

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Sporadic Goiter Due to Hypothyroxinogenesis. Report of Four Cases with Iodine Organification Defect [1]

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Biochemical data and genetic studies gradually accumulating are suggesting a defect in the hormonal synthesis as the principal factor in the pathogenesis of sporadic goitrous cretinism. Stanbury and Hedge (1950) described a group of goitrous cretins in which rapid elimination of the accumulated iodide by the administration of potassium thiocynate was observed. The existence of a defect in the iodide organification system leading to a deficiency in the production of iodotyrosines was demonstrated (Haddad and Sidbury, 1959; Schultz et al., 1957; Berand and Koralnik, 1959; Joseph et al., 1958; Lobo et al., 1960; Stanbury and McGirr, 1957). Further reports indicated various other defects in the hormonal synthesis: iodide trapping defect (Stanbury and Chapman, 1960); iodotyrosine dehalogenase defect (Choufoer et al., 1960); iodotyrosil--coupling defect (McGirr et al., 1956); and production and release by the thyroid of iodoprotein without hormonal activity (DeGroot et al., 1958). The occurrence of inbreeding in some families of goitrous cretins suggested a genetic basis for these conditions (Stanbury and Querido 1956). The occurrence of deafmutism in association with goitrous cretinism, long ago described as the Pendred syndrome, might be explained on a genetic basis. It is not clear, however, if one or two connected genes could be responsible for alteration in tissues of different embryological origin (Trotter, 1960).

In this report four cases of iodide organification defect of the thyroid are described.

METHODS

The protein bound iodide (PBI^{127}) was estimated in serum by a modification of Barker's method (Barker et al., 1951). The radioactive iodide uptake was measured at first 2 and 24 hours after oral intake of radioactive iodide (I^{131}); afterwards the perchlorate test was performed according to the following technique: after the given tracer dose of I^{131} repeated countings, every 15 minutes, are done until steady readings are obtained (90 to 120 minutes); then, two grams of potassium perchlorate suspended in glucose water are administrated orally, the countings being repeated at the same intervals. The curves obtained are then compared with the control curves without perchlorate. Chromatographic studies were carried out on blood collected with propylthyouracil and thymol 48 hours after the administration of 200 to 300 microcouries of radioiodine. The serum was extrated three times with n-butanol satured with 5 per cent sodium thiosulfate and acidified with hydrochloric acid 0,1 N v/v. Extracts were collected and drops of 2 N ammonia were added, and vacuum evaporation under 50°C was carried out.

The residuum and iodide, monoiodotyrosine (MIT), diiodotyrosine (DIT), 3,5,3 — triiodo, d,l — tyrosine (T3) and l — thyroxin (T4) carriers were chromatographed on Whatmann n. 1 paper using n-butanol acetic acid-water (40-10-50) and n-butanol ammonia (50-50) for 18 hours, after 12 hours of equilibrium at 32°C. The dried chromatographic stripes were stained with Pauly's reagent cut in 1 cm pieces and measured in a well-counter. The results plotted on an arithmetic scale are presented in the table.

CASE REPORT

Case 1 — APFS, HC-623084, aged 20, white unmarried male, coming from an area without endemic goiter. No inbreeding in the family. Born after normal pregnancy but protracted labour; didn't cry at birth and seemed cyanotic. No suction reflex. No goiter was observed then. Soon, obstipation, lethargy and anorexia appeared. The skin became pale, coarse and dry; the hair dry and coarse. Desiccated thyroid treatment (30 mg daily) was starded 8 days after birth. Increasing goiter was noted at 3 years of age in spite of higher doses of thyroid administered (40 to 60 mg daily). Normal growth but slow mental development. Puberty at 12. Because of agressiveness thyroid therapy was withdrawn at 14, and the patient was sent to a mental hospital. On physical examination, the patient looked well-nourished and fat. Facies

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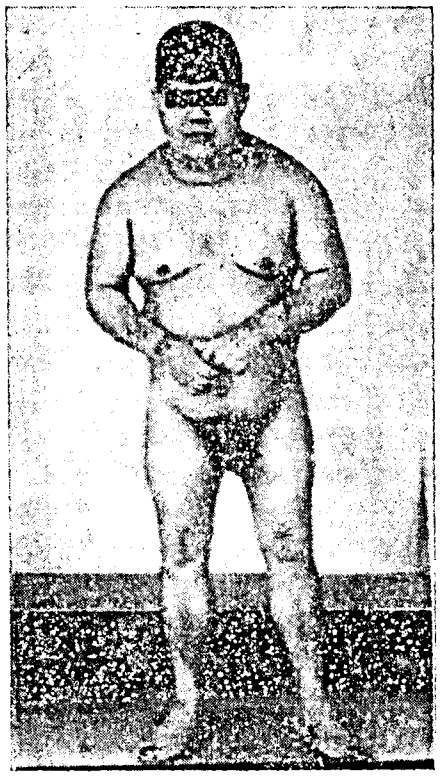

Fig. 1

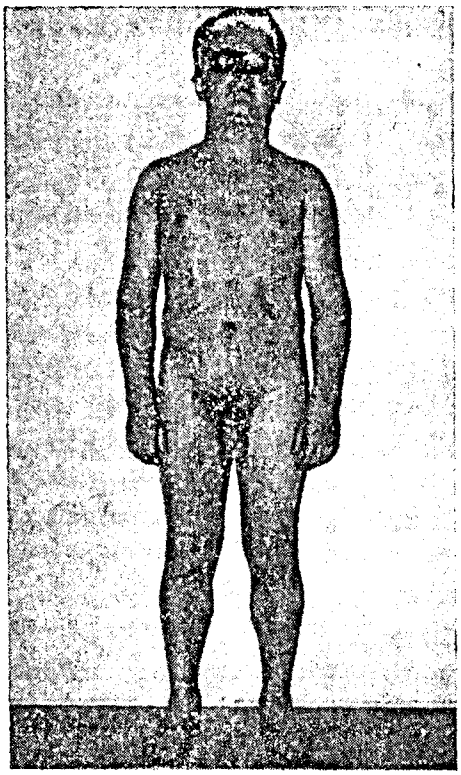

Fig. 2

suggesting *cretinism*. Coarse and dry skin. Myxedema. Short and thick neck. Conspicuous, firm and diffuse goiter. Normal genitals. Wt. 71k; Ht. 1.41m; *epu* 1.48 *m*. Blood pressure 95 x 60mm/Hg. Pulse 76/min.

Case 2 — JFLG, HC-399.196, aged 23, white unmarried male, from the Portughese Island of Madeira. Born after normal pregnancy and labour. Normal somatic and mental development. Rapidly increasing goiter was observed at 10. Iodide administration apparently intensified the rate of goiter growth. After sub-total thyroidectomy performed at 16, obstipation, lethargy dryness and coarseness of the skin, brittleness of hair and of linear growth were noted. No inbreeding in the family. Brother aged 15 shows similar symptoms (case 3). On physical examination the patient looks well-nourished and fat. Dry and coarse skin and hair. Hoarse voice. Thyroidectomy scar is visible on the anterior cervical region. Firm, diffuse and painless goiter is palpable. Normal genital and sexual development. Wt. 60k Ht. 1.56m. Blood pressure 100/70mm/hg. Pulse 84/min.

Case 3 — JRLG, HC-660.912, aged 15, white male boy, from the Portughese Island of Madeira. Born after normal pregnancy and labour. Subnormal mental and somatic development. At four years of age the patient was fat and mentally retarded. On physical examination he looked fat and well-nourished with the coarse features

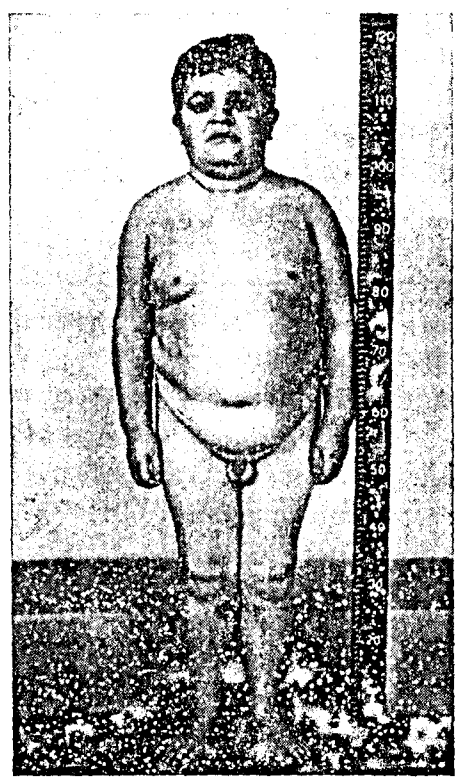

Fig. 3

of cretinism. The skin was pale, cool, rough, coarse and dry. Thick and short neck. Diffuse and firm goiter. Sexual infantilism (fig. 3) Wt. 48k. Ht. 1.19m. Blood pressure 110 x 70mm/Hg. Pulse 84 min.

Case 4 — JFS, HC-661.010, aged 5, white male, born after normal pregnancy and labour. Normal somatic and mental development. Generalized convulsion occured at 9 months. Since then on anti-convulsive therapy. Goiter was noted at 2 years. After treatment with iodide and thyroglobulin, further enlargement of goiter was observed. At 3, linear growth appeared stunted. The father lived in an endemic goiter area and had noted a goiter at puberty. No inbreeding in the family. On physical examination he seemed rather small. Diffuse goiter of normal consistency was palpable. Wt. 14.3k. Ht. 1.00m.

Table and figure 5 show the results of laboratory data.

DISCUSSION

The 2-hours I^{131} uptake was higher than the normal average (12 — 4,8%) in all patients except for case 2 (see Table). The rapid elimination of accumulated iodice in the gland, suggesting a defect in the organification process, was confirmed by perchlorate test. The serum PBI^{127} in all cases was consistent with the values usually found in hypothyroidism. Cases 2 and 4 showed clinically signs of mild hypothyroidism, the full picture of cretinism being evident only in cases 1 and 3. Response to perchlorate test in case 2, clinically suggesting partial defect in hormonal synthesis, was similar to the response found in cretins (cases 1 and 3). It is therefore difficult to correlate the response to the perchlorate test with the intensity of clinical manifestations of hormonal deficiency. Total block in hormonal synthesis was apparently confirmed by serum chromatography in case 1 in which it was not possible to detect any hormonal compound (see Table). In cases 2, 3 and 4 the serum chromatography revealed the presence of T3 and T4. In case 3, DIT was detected in serum, suggesting the possibility of a concomitant defect in dehalogenation of iodotyrosines with subsequent output of iodinated aminoacids in the circulation. The thyroid enlargement noted in cases 2 and 4,

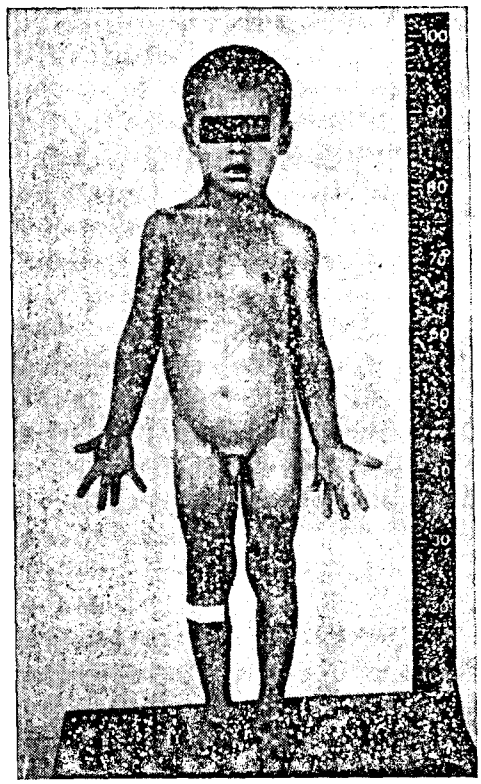

Fig. 4

Patient	Age (Years)	Sex	Height (cm) Weight (kg)	Bone Age (Years)	Radioactive iodine uptake (hours)	127 PBI meg/100 ml	Serum chromatography	Previous treatment	Clinical picture
Case 1 A.P.F.S.	20	M	148 71	18	2 h = 72%D 24h = 17%D	1.9	Iodide	Thyroid extract	Cretinism
Case 2 J.F.L.G.	24	M	156 60	18	2 h = 42% 24h = 54%	1.7	T3 and T4	Iodine surgery	Hypothyroidism
Case 3 J.R.L.G.	15	M	119 43	5	2 h = 74% 24h = 28%	0.5	Iodide T3, T4 and DIT	Cytomel (T3)	Cretinism
Case 4 J. F. S.	5	M	100 14	1.5	2 h = 70% 24h = 25%	2.6	T3 and T4	Thyroid extract	Hypothyroidism

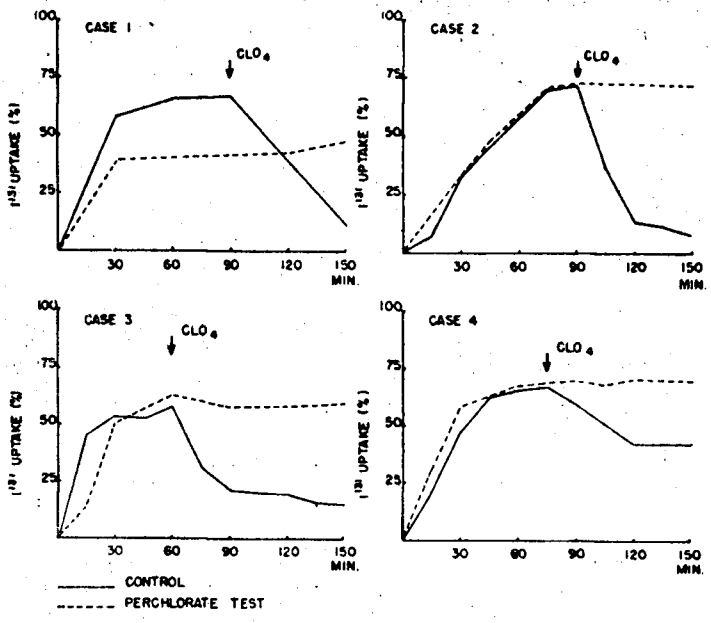

Fig. 5 — Perchlorate was administered after the 131I uptake peak was reached. A sharp fall in the thyroid radioactivity was observed.

after iodide medication, is difficult to be explained. Wiener and Lindeboom (1963) showed that the ability of the thyroid to convert the trapped iodide into iodine compounds was greatly diminished during desiccated thyroid therapy in euthyroid woman with an excessively large goiter. A similar defect has been encountered in patients taking large amounts of inorganic and organic iodine compounds (Paris et al. 1960; Oppenheimer and McPherson, 1961; Dowling and Becker, 1960; Paley et al., 1958).

An excessive administration intensifying a pre-existing defect, could be responsible for the enlargement observed in our cases. In three families studied there was no history of inbreeding and no occurence of familial goiters. The similar organification defect present in two brothers (case 2 and 3) suggests the existence of a recessive gene in both parents. Stanbury and Hedge (1950) pointed out the existence of a similar defect in three cretins in a family with seven siblings. In others reports (Haddad and Sidbury, 1959; Stanbury and McGirr, 1957) occurrence of more than one case in the same family was pointed out.

SUMMARY

Four cases of sporadic goiter due to hypothyroxinogenesis were studied. Perchlorate test was positive in all patients, indicating an iodide organification defect. Chromatographic studies showed complete hormonal synthesis block in one case; in the other three patients T3 and T4 were detected. In the course of iodide therapy an enlargement of the goiter was noted in two cases; the probable mechanism is discussed.

RESUMO

Bócio Esporádico Devido a Hipotiroxinogênese. Relatório de Quatro Casos com Defeito de Organificação de Iodeto.

Vários tipos de defeitos de síntese dos hormônios tireoidianos foram descritos:

1) Ausência da captação do iodeto, na presença de tecido tireoidiano.

2) Ausência ou diminuição da organificação do iodeto por impedimento de ação ou falta da citocromo-oxidase ou presença, em circulação, de bloqueadores de síntese.

3) Ausência ou impedimento da "acoplase", enzima que promoveria o acoplamento de dois grupos iodo-tirosil para a formação de tiroxina ou de triodotironina.

4) Diminuição ou ausência da ação de desalogenases, enzimas que promovem a desalogenação de grupos tirosis inativos, porém iodados, durante a proteólise da tireoglobulina. O iodo assim obtido, livre da molécula orgânica, é reciclado dentro do folículo tireoidiano.

5) Defeito na proteólise da tireoglobulina, originando produtos não totalmente hidrolisados, como são os polipéptidos iodados, que não têm ação hormonal.

As características dêstes casos de disormoniogênese são representadas pela maior incidência familiar e pelo maior índice de consangüinidade. Clìnicamente, os pacientes apresentam bócios que regridem, com muita facilidade, com o tratamento hormonal. São hipotireoidianos e costumam aparecer em zonas em que o bócio não é endêmico.

O tratamento pela tircoidectomia, como no caso 2, é seguido por um reaparecimento rápido do bócio devido à hiperplasia e hipertrofia do tecido restante.

Os autores apresentam quatro casos de defeitos de síntese do hormônio tireoidiano devidos à provável falta de citocromooxidase. Foram feitas análises da iodemia protéica, testes de captação do ^{131}I e de descarga do ^{131}I acumulado na tireóide pela administração de perclorato de potássio. O teste de perclorato positivo faz o diagnóstico dêste tipo de defeito de síntese, o que ocorreu nos quatro casos estudados. A análise cromatográfica dos aminoácidos iodados do sôro dos pacientes revelou graus variáveis na queda da organogênese do ^{131}I, o que estava de acôrdo com o grau de hipotireoidismo dêstes pacientes. Em um dos casos (caso 3) havia, cromatogràficamente, a presença em circulação de di-iodotirosina, sugerindo a concomitância de outro tipo de defeito de síntese.

RÉSUMÉ

Le goitre sporadique causé par l'Hypothyroxinogenèse.

Ce travail a pour objet la description de plusieurs anomalies relatives à la synthèse des hormonnes thyroidiennes, à savoir:

1) L'absence de fixation de l'iodure au contact du tissu thyroidien.

2) L'absence ou le ralentissement de l'intégration de l'iodure par suite du blocage ou de l'absence de la cytochromo-oxydase, ou sous l'action de "bloqueurs" de synthèse, en circulation dans le sang.

3) L'absence ou le blocage de "l'accoplase", enzyme qui effectuerait "l'accouplement" de deux groupes iodo-thyrosil d'où dériverait, soit de la thyroxine, soit de la triodothyronine.

4) L'action ralentie ou nulle des désallogénases, enzymes qui provoquent la "désallogénation" des groupes thyrosils inactifs (quoique iodés), durant la protéolyse de la thyréoglobuline. L'iode ainsi obtenu, libéré de la molécule organique, est recyclé à travers le follicule thyroidien.

5) La protéolyse défectueuse de la thyréoglobuline, donnant naissance à des produits incomplètement hydrolysés tels que les polypeptides iodés, dépouvus d'action hormonale.

Ces cas de dyshormonogenèse ont ceci de particulier que leur indice de fréquence est fonction de la parenté et du degré de consanguinité. Au point de vue clinique, les goitres dont les malades sont affligés se résorbent très facilement par le traitement hormonal. Les patients sont hypothyroïdiens et se trouvent surtout dans les règions où le goitre n'est pas endémique. Le traitement par thyroïdectomie (cas 2.) n'empêche pas le retour rápide du goitre du à l'hyperplasie et à l'hypertrophie du tissu restant.

Les auteurs mentionnent 4 cas où il semble que le défaut de synthèse doive être attribué à l'absence de cytochromo-oxydase. Les analyses de l'iodémie protéique ont été effectueés ainsi que des tests de captage et d'élimination du ^{131}I accumulé dans la thyroïde par administration de perchlorate de potassium. Le test de perchlorat, positif dans les 4 cas, prouve qu'on a affaire au défaut de synthèse type 2. L'analyse chromatographique a révélé la présence dans le sang de di-iodothyronine, ce que l'on ne peut expliquer qu'en admettant l'existence simultanée d'un autre type de défaut de synthèse.

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