Familial Thyroxine-binding Globulin Deficiency

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Summary: Genetically determined thyroxine-binding globulin deficiency is described in two families in the United Kingdom. All subjects in both pedigrees were euthyroid. Transmission was by sex-linkage; males showed low serum protein bound iodine and high thyroxine (T₄) resin uptake due to complete absence of serum thyroxine-binding globulin; females were less severely affected. The distinctive biochemical results disclosed the diagnosis and emphasize that serum protein bound iodine levels should be interpreted carefully and tests, such as triiodothyronine (T₃) or T₄ resin uptake, used to prevent erroneous diagnoses of hypothyroidism.

Introduction

A low serum protein-bound iodine (P.B.I.) level due to decreased thyroxine-binding globulin (T.B.G.) in a euthyroid subject was first recorded by Tanaka and Starr (1959). Several reports of familial instances of this condition followed (Nicoloff *et al.*, 1964; Marshall and Levy, 1966; Nikolai and Seal, 1966, 1967; Refetoff and Selenkow, 1968). Most of these studies indicate a sex-linked mode of transmission. There is, however, evidence for autosomal dominant inheritance (Nicoloff *et al.*, 1964; Kraemer and Wiswell, 1968) and for the occurrence of two different electrophoretic types of T.B.G. (Thorson *et al.*, 1966), each of which might be transmitted by a different genetic mechanism.

The low P.B.I. may lead to an erroneous diagnosis of thyroid dysfunction. A series of such cases has been reported by Nikolai and Roberts (1969), who discussed the differentiation of T.B.G. deficiency from actual thyroid disease and concluded that the combination of P.B.I. and a resin uptake test provides a useful criterion.

The following report is of two families in the United Kingdom, in each of which several members showed T.B.G. deficiency.

Methods

The P.B.I. ¹³²I neck uptake, and T₃ suppression tests were performed by standard methods. In this study serum thyroxine-binding capacity was measured by a T₄ resin uptake technique. Serum total T₄, T₄ resin uptake, and free thyroxine index were determined by the method of MacLagan and Howorth (1969). T.B.G. concentrations were estimated by electrophoresis on cellulose acetate of serum enriched with 210 µg. of ¹²⁵I-labelled T₄ per 100 ml. The buffer was tris maleate, pH 8.6, ionic strength 0.05. Electrophoresis was carried out for 40 minutes at 150 mvols. Good separation of T.B.G., thyroxine-binding albumin, and thyroxine-binding pre-albumin was obtained. The radioactivity bound to each protein fraction was measured by cutting the electrophoretic strip transversely into 2-mm. sections and counting the

activity in each section in a well-type scintillation counter. T.B.G. concentrations were expressed as T₄ bound in µg. per 100 ml. of serum.

Family Studies

Family 1.—The proband, a 21-year-old man, presented with tiredness of one month's duration. Positive findings were moist, warm hands and a sinus tachycardia. A P.B.I. test was performed to exclude thyrotoxicosis. The value was remarkably low at 2.3 µg./100 ml. Further tests of thyroid function were performed on the proband and his family (Fig. 1, Table I). In

addition, the basal metabolic rates were determined in Cases 1, 2, and 3, and were, respectively, 117%, 98%, and 100%. The four-hour ¹³²I neck uptake values for radioiodine were as follows: Case 1 18%, Case 2 17%, and Case 3 14%. In Case 1, after seven days on triiodothyronine 20 µg. q.i.d., the four-hour neck uptake had fallen from 18 to 8% (normal range for four-hour ¹³²I is 7-30%).

Family 2.—The proband was a 66-year-old woman. She was investigated for myxoedema in 1967 because she complained of depression and "feeling the cold." A ¹³²I neck uptake of 30%

in four hours and a normal serum cholesterol of 230 mg./100 ml. refuted the diagnosis. Further tests, however, suggested T.B.G. deficiency, and the family was studied (Fig. 2, Table II).

Results

The indices of thyroid function are presented in the tables. Cholesterol values are not tabulated as they were normal in both affected and unaffected family members. Similarly,

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TABLE I.—Thyroid Indices in Family 1

Case No.	Relationship	P.B.I. (μg./100 ml.)	Serum Total T4(μg./100 ml.)	T4 Resin Uptake	T4 Free Thyroxine Index	T.B.G. (μg.T4 bound/ 100ml.)
	Normal range	4-8	4-11	0.92-1.19	4.16-11.4	18-26
1	Propositus	2.5	3.2	<i>Affected Males</i>		
2	Brother	3.0	1.1	1.92	6.1*	0
3	Brother	2.8	1.5	2.12	2.3*	0
17	Maternal grandfather	1.0	0.8	1.65	2.5*	0
				2.08	1.67*	0
				<i>Affected Females</i>		
12	Mother	4.8	5.2	1.16	6.0	20
13	Aunt	4.4	7.9	1.17	9.2	23
16	Aunt	4.8	7.6	1.20	9.1	22
32 cases		4.4-7.3	4.6-11.8	0.9-1.14	4.5-11.8	18-26

*Result invalid because of low T.B.G. level (see text).

TABLE II.—Thyroid Indices in Family 2

Case No.	Relationship	P.B.I. (μg./100 ml.)	Serum Total T4(μg./100 ml.)	T4 Resin Uptake	Free Thyroxine Index	T.B.G. (μg.T4 bound/ 100 ml.)
2	Brother	2.3	0.4	<i>Affected Males</i>		
3	Brother	2.3	1.3	3.36	1.3*	0
4	Brother	2.2	2.4	2.51	3.3*	0
				2.53	6.1*	0
1	Propositus 1967	—	<1.0	<i>Affected Females</i>		
	" 1969	2.3	1.0	1.97	<1.97*	—
5	Niece	2.6	5.5	2.2	2.2*	12
6†	Niece	3.4	3.1	1.67	8.8*	13
7	Niece	5.0	4.5	1.18	3.7	24
8‡	Niece	4.1	5.1	1.18	5.4*	13
				1.20	6.1	21
9	Nephew	6.5	9.3	<i>Unaffected Cases</i>		
				1.05	9.8	21

*Result invalid because of low T.B.G. level (see text).
†On oral contraceptive pill.
‡Three months after gestation.

serum protein electrophoreses were normal throughout both families, showing that T.B.G. deficiency is a specific entity and not part of a generalized protein disturbance.

The genetic relationships between affected members of each family are shown in Figs. 1 and 2. Genetic linkage information was sought to help in mapping the locus of the T.B.G. gene on the X chromosome. In this project two sex-linked genetic characters—namely, red-green colour vision and the blood group Xga—were studied in all members of both families for use as genetic markers. Xga blood group failed to segregate in either family, all members being Xga positive. There was no person in whom T.B.G. deficiency and red-green colour blindness occurred on the same X chromosome. Hence no data concerning the proximity of the T.B.G. locus to either of the marker genes were forthcoming.

Discussion

In both families the affected males showed complete absence of T.B.G., low P.B.I., and high T4 resin uptake. There was no instance of father-to-son transmission. Females were less severely affected and might have been difficult to separate from normal subjects in the absence of a family history as noted by Marshall and Levy (1966). They had intermediate levels of T.B.G. ranging from low to normal. Their P.B.I. values were low or at the lower end of the normal range. Their T4 resin uptake values were high or at the upper end of the normal range. All daughters of T.B.G.-deficient fathers were affected, though the severity of affection showed considerable variation in the females of Family 2 and was greater than in the females of Family 1. These data are indicative of sex-linked inheritance.

The normal T3 suppression test disproved the suspicion of thyrotoxicosis in the propositus of Family 1. In Family 2 the index case has confirmed her euthyroid status by remaining fit and well for three years without replacement therapy. In both cases the clinical suspicion of thyroid disease was unfounded

but led to the recognition of T.B.G. deficiency. Recently, two other families have come to our notice. Possibly, therefore, the condition is not rare but remains largely undetected in the population.

The diagnosis can be confirmed by the distinctive biochemical results, which differ from those seen in other forms of thyroid dysfunction. Thus in myxoedema the P.B.I. and T4 resin uptake are low and in thyrotoxicosis both are high, while in T.B.G. deficiency P.B.I. is low and T4 resin uptake high. The total serum T4 level parallels the P.B.I. in these cases and has the advantage of freedom from interference by iodine-containing drugs. It is apparent from published series that the more commonly used T3 resin uptake test gives results which parallel those of the T4 resin uptake test used in this study. The T4 free thyroxine index is the product of T4 resin uptake and serum total T4. It was devised to compensate for minor alterations in serum-binding capacity and is, in general, superior to either of its constituents in defining thyroid status (Howorth and MacLagan, 1969). The theoretical validity of the T4 free thyroxine index, however, is transgressed if T.B.G. is absent or very low. Hence, T4 free thyroxine index in common probably with other types of free thyroxine index should not be applied to the situation of T.B.G. deficiency.

Genetic alterations in T.B.G. concentration may lead to diagnostic errors if unrecognized. Clinical judgement together with selected thyroid function tests can establish the correct diagnosis in most instances. Should thyroid disease coexist with T.B.G. deficiency, the position is best elucidated by tests which are independent of serum-binding factors, such as the basal metabolic rate, serum cholesterol, and radioiodine uptake studies.

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Preliminary Communications

Paper Chromatographic Survey of Urinary Amino-acids in Muscular Dystrophy

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Summary: A paper chromatographic analysis in 60 patients with muscular dystrophy from 49 families and in 351 of their relatives showed a high incidence of generalized hyperaminoaciduria in both patients and relatives. There was a higher incidence of threoninuria in patients and their relatives than in controls. One family was found to have excess histidinuria and another excess lysinuria.

INTRODUCTION

The frequency and significance of abnormal amino-aciduria in muscular dystrophy is at present controversial. Partial or universal hyperaminoaciduria has been found in patients with muscular dystrophy (Ames and Risley, 1948; Schöenberg, 1955; Berger, 1962) and unaffected relatives (Blaht *et al.*, 1955; Beckmann and Ritter, 1967). A basic hyperaminoaciduria has been described in a family in which there were several members affected with facio-scapulo-humeral muscular dystrophy (Hurwitz *et al.*, 1965, 1967). A similar pattern of amino-aciduria has also been reported in four out of five siblings with severe congenital muscular hypotonia (Clara and Lowenthal, 1965). Some authors have found an excess amino-aciduria restricted to leucine and taurine and possibly threonine and valine (Hurley and Williams, 1955) and to arginine, threonine, and proline. There have, however, also been studies in which there was no excess amino-aciduria in muscular dystrophy (Bickel and Souchon, 1955; Carver *et al.*, 1961). The present survey attempts to determine the incidence and pattern of hyperaminoaciduria in patients with muscular dystrophy and in their relatives, using a paper chromatographic screening technique.

METHODS

Urinary amino-acids were analysed by paper chromatography, using a technique described by Carson and Neill (1962), in patients with muscular dystrophy residing in North-

ern Ireland and their relatives. Since dietary and environmental factors are known to have a profound effect on amino-acid excretion written instructions were given to all subjects, stating that the urine sample should be produced in the morning before breakfast, and during the mid-menstrual cycle in the case of women. A health visitor collected the samples on the day on which they were provided. The subjects were instructed to notify her of any unusual dietary intake and medications but to endeavour to provide the specimen when there was no unusual food intake. Two or three samples were collected from subjects at about monthly intervals. The urine specimens were stored at -25°C. until analysis.

The chromatographic procedures were rigorously standardized. The volume of urine applied to the paper was that equivalent to a standard amount of nitrogen. In addition to the urine sample, 5µl. of β-amino-octanoic acid was applied at the origin of each chromatogram. The β-amino-octanoic acid migrated to a position well away from the naturally occurring amino-acids. This was used as a standard, and the colour intensities of the urinary amino-acids after the ninyhydrin reaction were visually compared with that of the standard and given arbitrary units of intensity with a range of 1 to 5. This attempt at semiquantitation made the assessment of hyperaminoaciduria less subjective.

SUBJECTS

The propositus in each family was examined clinically and a provisional diagnosis made of the type of muscular dystrophy, except in the three families in which the propositus was not alive. An attempt was made to examine clinically all first-degree relatives, and detailed information was sought of any other relatives who might have muscle disease, and they were then examined or hospital documents obtained.

The clinical classification of the dystrophy is given in Table I. There were 36 male patients aged 7 to 68 years, 24 females aged 18 to 58 years, and 157 male and 194 female

TABLE I.—49 Families with Muscular Dystrophy

X-linked Duchenne	..	..	..	..	..	..	..	..	3
Resembling Duchenne	..	..	..	..	..	..	..	..	11
Facio-scapulo-humeral	..	..	..	..	..	..	..	..	7
Autosomal recessive limb girdle	..	..	..	..	..	..	..	..	20
Dystrophia myotonica	..	..	..	..	..	..	..	..	6
Congenital myopathy	..	..	..	..	..	..	..	..	2