Familial Dyalbuminemic Hyperthyroxinemia: A Study of Four Probands and the Kindred of Three

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We investigated four probands, and the kindred of three, with familial dyalbuminemic hyperthyroxinemia, using the one- and two-step tests for free thyroxin and other thyroid-function tests. The results indicate that this is an autosomal dominant trait. The discovery of eight cases in our patient population, which represents about 4% of our hyperthyroxinemic patients (8/220), during eight months indicates that this aberration is more prevalent than suspected. Its importance lies in the misinterpretation of test results and the consequent inappropriate treatment for thyrotoxicosis.

Additional Keyphrases: heritable disorders · thyroid status

Familial dyalbuminemic hyperthyroxinemia (FDH) is a recently described autosomal dominant syndrome in which euthyroid patients have above-normal values for TT₄ in serum, FT₄, and FT₃ by a single-step radioimmunoassay (RIA). These findings are caused by preferential binding of T₄ to an abnormal albumin rather than to the hormonal-binding sites on thyroxin-binding globulin (1). The FT₄ value is normal in these patients when measured by a two-step RIA kit method or the more cumbersome equilibrium dialysis method.

We have studied four such patients and the kindred of three—the fourth refusing any further investigation—and have verified these findings.

The importance of FDH lies in the fact that these above-normal laboratory test results have been interpreted as indicating thyrotoxicosis and, consequently, patients have been erroneously treated. To date, only about 58 patients have been reported (2–7), but we believe the syndrome to be more prevalent than the literature suggests.

Materials and Methods

The subjects were among those patients referred to the clinical laboratory by their physicians for routine assessment of their thyroid metabolic status. In our laboratory, the initial thyroid evaluation study is the one-step determination of FT₄ in serum, performed with the Clinical Assays (Cambridge, MA) RIA kit. The method is based on the competitive-binding principles of RIA. In this procedure serum is incubated with a I²I₄]thyroxin analog ([I²I₄]TT₄ analog) tracer, in tubes coated with a precise amount of firmly adhering antibody. The radioactive tracer does not significantly interact with the binding proteins in serum. After the incubation of 90 min at 37 °C, the T₄ (labeled and unlabeled) bound to the immobilized antibodies is separated from the unbound T₄ by either aspiration or decantation. A standard curve is prepared from data on five serum-based standards, and the unknown values are interpolated from the standard curve. The FT₄ in the test serum is inversely proportional to the concentration of tracer T₄ bound to the antibody-coated tube.

In the above procedure, if the FT₄ value exceeds approximately threefold the upper limit of our normal reference interval (6–19 ng/L), a two-step FT₄ procedure (Clinical Assays) is performed. In this procedure, the serum is first incubated in the antibody-coated tubes; the FT₄ is bound to the antibody coated on the tube, and the T₄ bound to the serum proteins is decanted or aspirated. The tubes are rinsed with a buffer solution and again incubated, this time with added [I²I₄]T₄ tracer in the buffer. The tubes are aspirated or decanted again and the radioactivity is quantified. The unknown values are interpolated from the appropriate standard curve.

We measured TT₄ and thyroxin-binding globulin with Clinical Assays RIA kits. RT₃U was evaluated by BioScience Laboratories, Honolulu, HI.

Results

One of us (A.G.S.) examined the medical records of each patient. The test results were discussed with the attending physicians. To their knowledge, none of the patients had any evidence of thyroid disease, and none was receiving any medication. Results of thyroid-function tests are tabulated in Table 1. The normal reference intervals were derived from values for healthy men and women attending our multiphasic screening program.

We attempted to study the kindred of all four subjects but were unsuccessful in getting data from one patient (G.M.), whose immediate family was not available. Results of thyroid-function tests for the kindred of the remaining three patients are also presented in Table 1 with corresponding pedigrees in Figure 1. We find that at least one member of a previous or subsequent generation has FDH. In the case of J.R., both situations pertain—that is, her father and daughter are affected—confirming the impression that the mode of transmission is by an autosomal dominant gene. As with the propositi, the affected members have normal results for corroboratory thyroid-function tests, viz., serum FT₄ (two-step method), RT₃U, and thyroxin-binding globulin.

Discussion

FDH, a recently discovered syndrome, is relatively unknown to many clinicians. We believe it to be more common than previously suspected. Its importance is that these patients are mistakenly thought to be thyrotoxic by their physicians when in fact they are euthyroid. Some have even been treated (8).

The features and pathophysiology have been described previously (1, 3–5). The increase in TT₄ is due to the presence of an abnormal albumin in the serum of the affected patients. The hormonal-binding sites on this abnormal albumin have a much greater affinity for T₄ than do the hormonal-binding sites on thyroxin-binding globulin. These

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3 Nonstandard abbreviations: FDH, familial dyalbuminemic hyperthyroxinemia; T₄, thyroxin; TT₄, total thyroxin; FT₄, free thyroxin; FT₃, free thyroxin index; RT₃U, resin uptake of radioactive triiodothyronine.

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Table 1. Thyroid Function Test Results for Four Patients (*) with FDH and Some of Their Kindred

<table>
<thead>
<tr>
<th>Subjects</th>
<th>1-step</th>
<th>2-step</th>
<th>FT4, ng/L</th>
<th>TT4, µg/L</th>
<th>T3, mg/L</th>
<th>TBG, mg/L</th>
<th>RT³, U ratio</th>
<th>FT4</th>
</tr>
</thead>
<tbody>
<tr>
<td>*L.R.</td>
<td>6.1</td>
<td>1.6</td>
<td>156</td>
<td>1.48</td>
<td>15.0</td>
<td>1.14</td>
<td>18.5</td>
<td></td>
</tr>
<tr>
<td>G.R. (spouse)</td>
<td>1.6</td>
<td>ND</td>
<td>119</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>L.R. (son)</td>
<td>1.4</td>
<td>ND</td>
<td>97</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>J.R. (daughter)</td>
<td>&gt;5.2</td>
<td>1.5</td>
<td>182</td>
<td>ND</td>
<td>24</td>
<td>0.91</td>
<td>16.6</td>
<td></td>
</tr>
<tr>
<td>M.T. (father)</td>
<td>6.4</td>
<td>1.8</td>
<td>117</td>
<td>1.41</td>
<td>12.0</td>
<td>1.01</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>M.T. (mother)</td>
<td>1.00</td>
<td>ND</td>
<td>78</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>D.S. (daughter)</td>
<td>1.4</td>
<td>ND</td>
<td>89</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>B.T. (brother)</td>
<td>1.5</td>
<td>ND</td>
<td>82</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>*J.R.</td>
<td>&gt;5.2</td>
<td>1.9</td>
<td>145</td>
<td>1.85</td>
<td>23.0</td>
<td>0.93</td>
<td>13.5</td>
<td></td>
</tr>
<tr>
<td>J.T. (father)</td>
<td>&gt;5.2</td>
<td>1.2</td>
<td>132</td>
<td>ND</td>
<td>25.0</td>
<td>0.97</td>
<td>12.8</td>
<td></td>
</tr>
<tr>
<td>A.T. (mother)</td>
<td>1.3</td>
<td>ND</td>
<td>92</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>T.L.R. (daughter)</td>
<td>&gt;5.2</td>
<td>1.9</td>
<td>149</td>
<td>ND</td>
<td>25.0</td>
<td>0.94</td>
<td>14.0</td>
<td></td>
</tr>
<tr>
<td>*G.M.</td>
<td>&gt;6.2</td>
<td>1.8</td>
<td>200</td>
<td>1.77</td>
<td>12.0</td>
<td>1.06</td>
<td>21.2</td>
<td></td>
</tr>
<tr>
<td>Normal ref.</td>
<td>6-19</td>
<td></td>
<td>45-115</td>
<td>0.8-2.2</td>
<td>13-30</td>
<td>0.82-1.19</td>
<td>3.7-13.7</td>
<td></td>
</tr>
</tbody>
</table>

ND, not done; T₃, triiodothyronine; TBG, thyroxin-binding globulin.

abnormal-binding sites are not found on all the albumin molecules. Ruiz et al. (8) have shown by filter-paper electrophoresis of serum enriched with a tracer concentration of [¹³¹I]T₄ that a much higher concentration of the label was associated with albumin in serum from patients with FDH than in serum from normal controls. This was true of all 15 of their patients. In addition, the percentages of [¹³¹I]T₄ associated with thyroxin-binding prealbumin and thyroxin-binding globulin were correspondingly decreased.

Using a tracer concentration of [¹³¹I]triiodothyronine in the same manner, these authors found a small but significant increase in the proportion of label bound in the albumin zone and a proportionate decrease in the thyroxin-binding globulin zone in the serum from patients with FDH.

In contrast to our findings and those in previous studies, Ruiz et al. (8) reported significantly higher concentrations of total triiodothyronine and a significant decrease in the proportion of free triiodothyronine in the abnormal sera.

The one question that requires an explanation is why the one-step FT₄, like the TT₄, gives an above-normal value for the concentration while the two-step method does not.

Reference to the section on Materials and Methods will answer that question. In the one-step FT₄ method, all ingredients — i.e., the test serum and [¹²⁵I]T₄ analog — are added concurrently into a single antibody-coated test tube. The labeled analog, which does not bind to normal albumin, is avidly bound by the abnormal albumin; hence, less is bound to the antibody-coated tube and less radioactivity is measured when the contents are decanted and the tube's radioactivity is counted. Because the serum T₃ concentration and radioactivity are inversely related, the serum FT₄ concentration is read as being correctly but artifactually above normal. In the two-step method, the test serum is first introduced into the antibody-coated tube; after a suitable period of incubation the serum is discarded, the coating of the tube washed, and the radiolabeled material introduced. Again, after a designated incubation interval, the contents are decanted, the tube coating is washed, and the amount of residual radioactivity is determined. In brief: the two-step method does not permit contact between the labeled T₄ and the abnormal albumin in the patient's serum.

Another recently described abnormality that can be confused with FDH is hyperthyroxinemia due to increased serum thyroxin-binding prealbumin. Moses et al. (9) have reported a father and son with euthyroid hyperthyroxinemia due to an increase in this protein. The laboratory findings are similar to FDH because the prealbumin binds T₄ but not triiodothyronine. Thus, the FT₃U is normal and the FT₄I is erroneously high, giving the impression of thyrotoxicosis. Similar laboratory findings have been reported in a patient with glucagonoma (10). Results of
immunohistochemical examinations of the islet cell tumor and metastastic tissue indicated that the excess prealbumin was produced by the tumor. Normally, the prealbumin and thyroxin-binding globulin are produced by the liver.

When thyroid-function tests—viz., an FT₄ (one-step), T₃, and (or) FT₃—I indicate hyperthyroxinemia, the immediate discrimination to be made is whether the patient has hyperthyrotoxicism or euthyroid hyperthyroxinemia. This can easily be done by appropriate testing—measurement of FT₄ (two-step or dialysis method) or total triiodothyronine. However, one must remember that the latter would be increased in the presence of increased thyroxin-binding globulin, in which case an assay for free triiodothyronine would also be indicated. Currently in our laboratory, the basic screening test for thyrometabolic status is the one-step FT₄. If results exceed threefold the upper limit of our normal reference interval, which is 19 ng/L, we then do the two-step test for verification. If the patient is found to be euthyroid, then one must determine to which of the many causes of euthyroid hyperthyroxinemia the case is to be ascribed. Borst et al. (11) have thoroughly reviewed this subject (Table 2 has been modified from their excellent review). Many of these causes are important but uncommon. The most commonly encountered causes are those related to increased thyroid-hormone binding, acquired and inherited.

In conclusion, we emphasize the importance for clinical awareness of this syndrome of FDH, namely, the avoidance of treating these patients with the mistaken diagnosis of thyrotoxicosis.

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References