Prevalence of Familial Dysalbuminemic Hyperthyroxinemia in Serum Samples Received for Thyroid Testing

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The prevalence of familial dysalbuminemic hyperthyroxinemia (FDH), a condition sometimes mistaken for hyperthyroidism, has not been clearly established. I present a study of the prevalence of FDH in serum samples received for thyroid-function tests in a reference laboratory. A prospective study of 15,674 serum samples was carried out over 24 months, of which 13,232 cases were from women (84.42%) and 2,442 were from men (15.58%). FDH was diagnosed in 26 cases, 22 in women and four in men. Therefore, the prevalence of FDH in the total number of samples from both sexes was 0.17%, 0.17% in women, and 0.16% in men, which is consistent with a dominant autosomal type of familial transmission. These findings demonstrate that cases of FDH occur frequently; therefore, every laboratory must be prepared to recognize them and thus avoid an incorrect diagnosis of the patient's thyroid function.

Additional Keyphrases: thyroid function • heritable disorders

Familial dysalbuminemic hyperthyroxinemia (FDH) is a clinical condition that has sometimes been mistaken for hyperthyroidism (1, 2). The patients with FDH are usually euthyroid subjects with high values for total thyroxin (T4), free thyroxin index (FTI), and results for the one-step free thyroxin (FT4) assays, whereas the results for total triiodothyronine (T3), T3 uptake (T3U), and the one-step free T3 assays are usually normal, as is the response of thyrotropin (TSH) to thyroliberin stimulation (3-5). High-sensitivity assays of TSH are useful in making this distinction.

The diagnosis of FDH can be more complicated in the presence of primary hypothyroidism or in cases of hypothyroidism secondary to treatment for factitious hyperthyroidism. In these conditions the patients have normal T4, FTI, and FT4 values, which makes FDH more difficult to recognize, because those affected are not hyperthyroxinemic (6). The final diagnosis in cases of FDH is obtained by the systematic use of in vitro tests to demonstrate an abnormal increase in the binding of T4 to the FDH albumin (7-9).

The prevalence of FDH has not been clearly established. Some have suggested that it may be a relatively frequent condition, because several families were reported, all with the same clinical and laboratory characteristics, in a short period of time (2, 4). Recently, Croxon et al. (10) suggested that “the wider use of in vitro thyroxin-binding tests will show many further examples of these recently described protein variants.”

Here I present a study of the prevalence of FDH in consecutive serum samples received for thyroid-function studies in a reference laboratory.

Materials and Methods

Specimens. Over a period of 24 months I carried out a prospective study of 15,674 consecutive samples of serum from patients (13,232 from women and 2,442 from men) for whom in vitro thyroid-function tests were requested.

The samples were obtained in our laboratory or received from other laboratories. Venous blood was collected in the morning and the serum was promptly separated by centrifugation. The serum samples were kept without additives at 4 °C, to be analyzed the same day, or frozen at -20 °C for longer storage.

Procedures. As an initial selection test, T4 binding to albumin was assessed on all samples after inactivation of thyroxin-binding globulin with acid, by a method previously published (11), the result of which was expressed as a T4-binding index and as T3U, determined by an in-house method with dextran-coated charcoal. The respective normal reference values for these methods were 0.90-1.11 and 25-35%.

Serum samples that yielded results within the corresponding normal reference range were not submitted to additional investigation, but only to the analyses required in each case. However, samples showing evidence of an increased binding of T4 to albumin underwent the following tests: T4, FT4, Amerlex M, TSH, and FTI (all from Amersham International, Amersham, Bucks, U.K.). The FTI was calculated by multiplying the T4 result by the T3U and then dividing by the T3 value of normal serum; in our laboratory the FTI reference range is 4.70-13.0. The abnormal binding of T4 to albumin was confirmed by augmenting the serum with unlabeled hormone (7) and by determining the “analog binding rate” after the one-step FT4 radioimmunoassay (12).

Results

Of the 15,674 serum samples analyzed, 26 exhibited FDH—22 from women (0.17%) and four from men (0.16%)—one case for every 600 samples analyzed. Of the 26 patients with FDH, 24 (92%) were euthyroid and two (8%) were hypothyroid with high TSH values (>10

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Nonstandard abbreviations: FDH, familial dysalbuminemic hyperthyroxinemia; T4, thyroxin; FT4, free thyroxin; FTI, free thyroxin index; T3, triiodothyronine; T3U, T3 uptake; and TSH, thyrotropin.
int. units/L); one of these two had a history of treatment with radioactive iodine. Neither of the two patients was receiving thyroid-hormone replacement treatment. Table 1 summarizes the results of the various thyroid-function tests for the patients with FDH. Table 2 shows the results of the tests used to demonstrate the abnormal binding of T₄ to the FDH albumin. In all the patients with FDH, T₃U always fell within the normal reference range for the method, demonstrating that FDH samples frequently exhibit an increased affinity exclusively for T₄.

Discussion

The prevalence of FDH determined in the samples routinely analyzed for thyroid-function studies in this reference laboratory confirms the observations made in several reports (2, 4, 10). These findings indicate that, unless some test is applied systematically to recognize the abnormal increase in the binding of T₄ to the FDH albumin, many patients with FDH remain undiagnosed, sometimes being mistaken for hyperthyroid subjects and treated as such. In my data, one patient was hypothyroid as a result of treatment with radioactive iodine. Surprisingly, although more than 12 years have gone by since the first case of FDH was reported (13), most of the physicians who treat patients with thyroid disease have not yet found cases of FDH. This condition, which is not accompanied by clinical symptoms, can be suspected only when the results of the thyroid-function tests do not correlate with the status of the thyroid patient. Consequently, each laboratory must draw up its own strategy to recognize the cases of FDH.

When the association of hyperthyroxinemia with a normal T₃U value is used as a selection criterion, most of the cases of FDH can be diagnosed. Nevertheless, patients with hypothyroidism and FDH would not be recognized because they have a normal T₄, a normal or low T₃U, and a high TSH, reflecting the thyroid deficiency (6). In my opinion, it is best to submit all the samples received for thyroid-function tests to some test that assesses the binding of T₄ to albumin, either by saturating the serum with nonradioactive T₄ (7) or after inactivating the thyroxin-binding globulin with acid and neutralizing it (11).

In the data analysis, the number of serum samples from women considerably exceeds that of the samples from men. Nevertheless, the prevalence of FDH was similar in both sexes, which is consistent with a familial transmission of a dominant autosomal type. Given the excess of women, the sample analyzed does not appear to be representative of the general population. The prevalence of FDH may therefore be overestimated because of the fact that a certain degree of selection is involved in the samples received in a reference laboratory for thyroid-function analysis; such samples often correspond to patients with a diagnosis of thyroid disease.

References


Table 1. Results of Thyroid-Function Tests in Patients with FDH

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference range</th>
<th>Euthyroid (n = 24)</th>
<th>Hypothyroid (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₄, µg/L</td>
<td>56–116</td>
<td>166.0 (141–212)</td>
<td>87.0 (71–103)</td>
</tr>
<tr>
<td>T₃U, %</td>
<td>25–35</td>
<td>29.67 (27.9–31.7)</td>
<td>27.35 (27.0–27.7)</td>
</tr>
<tr>
<td>FTI</td>
<td>4.70–13.5</td>
<td>16.50 (13.9–20.4)</td>
<td>7.90 (6.49–9.31)</td>
</tr>
<tr>
<td>FT₃, ng/L</td>
<td>6.5–19.0</td>
<td>41.60 (24.4–76.0)</td>
<td>17.60 (12.1–23.1)</td>
</tr>
<tr>
<td>TB, µg/L</td>
<td>0.8–1.9</td>
<td>1.50 (0.93–1.90)</td>
<td>1.34 (1.25–1.43)</td>
</tr>
<tr>
<td>TSH, mIU/L</td>
<td>0.3–6.0</td>
<td>2.12 (0.60–5.39)</td>
<td>22.00 (11.2–32.8)</td>
</tr>
</tbody>
</table>

* Based on the results for serum samples from 100 subjects (50 men and 50 women) with normal thyroid function.
* Mean (and range).

Table 2. Results Demonstrating Abnormal Binding of T₄ to Albumin in FDH Subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>n</th>
<th>Thyroxin binding index</th>
<th>Analog binding</th>
<th>% T₄ bound*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>20</td>
<td>1.00 (0.13)</td>
<td>1.00 (0.05)</td>
<td>89.7 (5.4)</td>
</tr>
<tr>
<td>FDH</td>
<td>26</td>
<td>4.12 (0.80)</td>
<td>0.56 (0.06)</td>
<td>51.1 (7.9)</td>
</tr>
</tbody>
</table>

* Percent of added T₄, 1 µmol/L, bound to charcoal.