STUDIES OF THE LIVER FUNCTION TEST IN VARIOUS DISEASES OF THE THYROID GLAND

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Structural and functional derangement of the liver has been noted in patients with hyperthyroidism (Cameron and Kurunaratne, 1935; Lichtman, 1953; Werner, 1955). Paul, in 1865, was the first to mention the association of hepatic cirrhosis and toxic thyroid disease. Jaundice was first mentioned by Haberson (1874). Kerr and Rusk, in 1922, reported acute yellow atrophy of the liver associated with hyperthyroidism. Anatomical changes in the liver in hyperthyroidism have been reviewed by many authors (Hashimoto, 1921; Haban, 1933; Rössle, 1933; Shaffer, 1940). Liver damage in experimental hyperthyroidism after feeding small or toxic doses of thyroid have been studied (Farrant, 1913; Althausen, 1932; Coggeshal and Green, 1933; Drill and Gun, 1944). Thyroid crisis have been attributed to hepatic insufficiencies by a number of observers (Dinsmore, 1937; Frazier and Frieman, 1935; Shaffer, 1940). Many investigators have reported that there is a clinical evidence of hepatic dysfunction obtained by utilization of liver function tests (Kugelmann, 1930; Hurxthal, 1933; Lichtman, 1941; Lord, 1941) in various grades of hyperthyroidism.

At present hepatic damage in hyperthyroidism may be attributed to four factors; the cytotoxic action of thyroid hormone (Farrant, 1913; Laurence and McCane, 1931; Coggeshall and Greene, 1933), unfavorable reaction to viral and bacterial infections (Haban, 1933; Lichtman, 1941; Sealy, 1941), the disturbance in circulation (Moschowitz, 1946; McArthur, 1947; Myer, Brannan and Holland, 1950) and in nutrition (Drill, 1937, 1940, 1944; Haines, 1941) which tend to complicate Graves' disease.

Hepatic disabilities can be cured to normal after successful treatment by operation or the use of antithyroid drugs unless the lesion is marked cirrhosis, so that laboratory tests should be performed in order to discover hepatic disabilities and causative factors and then to give prompt and intensive treatment. For this reason, it appears the most important point to decide which metabolism is more likely to be injured and which test is the most sensitive to detect it. The author performed various liver function tests in addition to liver enlargement and clinical signs in 37 patients of thyroid disease admitted to our hospital.

Thanks are due to the kind criticism and continous encouragement of Prof. K. Shichijio, under whose direction the present work was carried out.
PATIENTS AND METHODS

Various laboratory methods; basal metabolic rate, protein bound iodine and radioactive iodine procedures were used for the differentiation of thyroid diseases.

The group of thyrotoxicosis comprised of 9 males and 19 females. In most patients liver function tests were performed when they were admitted, but in several patients they were performed in 2 to 10 days after methylthiouracil treatment began. In the later group there was not such a great difference of basal metabolic rate compared to that in pretreatment. The average age was 33 years old, the youngest being 12 years and the oldest being 53 years. For the entire series of 28 patients with hyperthyroidism the basal metabolic rate ranged from +20 to +80 per cent, the average being +43 per cent. The duration of symptoms ranged from 8 months to 12 years, the average being 2.5 years.

Simple goiter was present in 7 cases, who were females. The average age was 22 years old, the youngest being 16 years and the oldest being 35 years. Basal metabolic rates ranged from -5 to +13 per cent, the average being +5 per cent.

Myxedema was present in 2 females, one is 54 and another is 42 years old.

Liver function tests performed were cadmium reaction (Inoue, 1952), thymol turbidity test, cephalin cholesterol flocculation test, half quantitative estimation of urobilinogen in the urine (Lephne modification), cobalt reaction (Inoue and Kumo, 1942), Takada—Jezler reaction, thymol flocculation test, bromsulphalein test, Gros reaction, zinc sulphate test, serum protein content (Yoshikawa, 1949) and Meulengracht icteric index. Blood used in these tests was always drawn up during fasting time. Basal metabolic rate was measured by the Knipping's method. Liver enlargement was measured below the costal margin in the right midclavicular line.

RESULTS

I. The result of liver function test in hyperthyroid patients

Functional disabilities of the liver were noted in 75 per cent of hyperthyroid patients (Table 1).

1) Liver enlargement. Slight or moderate enlargement of the liver (1 to 3 cm) was noticed in 15 out of 28 patients. The liver surface was smooth in 12 patients, firm in 10 and tender in none. In comparison with this result, liver enlargement was noticed only 72 out of 289 cases in normal subjects (Table 2).

2) Disturbance of protein metabolism (Table 3). Cephalin cholesterol flocculation test (C.C.F.); abnormal result of C.C.F. test was found in 14 patients. Grade of C.C.F. test was slight in 10 patients and moderate in 4 patients. Cobalt reaction: abnormal result of cobalt reaction was found in 14 patients; R5 in 8,

| Table 1. Functional Disturbance of the Liver in Various Diseases of the Thyroid Gland |
|---------------------------------|-------------------------------|-----------------|
| Number of Cases                | Number of Cases and Percentage of Positive Reaction for 12 Liver Function Tests | Per cent |
| Hyperthyroidism                | 28                           | 21              | 75   |
| Simple Goiter                  | 7                            | 1               | 14   |
| Myxedema                       | 2                            | 2               | 100  |
| Normal Subjects                | 289                          | 15              | 5    |
Table 2. Incidence of Liver Enlargement

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Cases</th>
<th>Number of Cases with Liver Enlargement</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroidism</td>
<td>28</td>
<td>15</td>
<td>53</td>
</tr>
<tr>
<td>Simple Goiter</td>
<td>7</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>Myxedema</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Normal Subjects</td>
<td>289</td>
<td>72</td>
<td>24</td>
</tr>
</tbody>
</table>

Table 3. Number of Cases and Percentage of Positive Reaction for Various Liver Function Tests in 28 Hyperthyroid Patients

<table>
<thead>
<tr>
<th>Test</th>
<th>Number</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.C.F.</td>
<td>14</td>
<td>50</td>
</tr>
<tr>
<td>Cadmium reaction</td>
<td>14</td>
<td>50</td>
</tr>
<tr>
<td>Cobalt reaction</td>
<td>14</td>
<td>50</td>
</tr>
<tr>
<td>T.T.T.</td>
<td>13</td>
<td>42</td>
</tr>
<tr>
<td>Urobilinogenuria</td>
<td>12</td>
<td>42</td>
</tr>
<tr>
<td>Gros reaction</td>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td>Takada-Jezler reaction</td>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td>B.S.P. test</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>Serum protein</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Meulengracht icteric index</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>T.F.T.</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Zinc sulphate test</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

R6 in 5, R7 in one patient. Cadmium reaction: slight or moderate abnormal result of cadmium reaction was found in 14 patients; R6 in 12, R4 in 2 patients. Thymol turbidity test (T.T.T.): abnormal result of T.T.T. was found in 13 patients; 5 units in 6, 6 units in 3, 7 units in one, 9 units in one, 10 units in one and 25 units in one patient. Gros reaction: abnormal result of Gros reaction was found in 9 patients; 1 plus in 5 patients, 2 plus in 3, 3 plus in one. Takada—Jezler reaction: abnormal result of Takada—Jezler reaction was found in 9 patients; 1 plus in 6 and 2 plus in 3. Thymol flocculation test (T.F.T.): abnormal result of T.F.T. was found in 4 patients; 9 units in one, 12 units in one, 14 units in one, 25 units in one patient. Zinc sulphate test: abnormal result of zinc sulphate test was found in one patient. Serum protein content: abnormal serum protein content was found in 5 patients; abnormal increase (9 to 9.8 g per 100 cc) in 4 patients and abnormal decrease (5.6 g per 100 cc) in one patient.

3) Disturbance of bile pigment metabolism. Half quantitative estimation of urobilinogen in the urine; 1 plus in 6, 2 plus in 6. Abnormal Meulengracht icteric index was found in 5 patients; 8 units in 3, 10 units in one, 11 units in one.

4) Disturbance of excretory function. Abnormal result of bromsulphalein (B.S.P.) test was found in 6 patients; 5 to 10 per cent of this dye in the blood after 45 mins. in 3, 10 to 15 per cent in 2 and 15 to 20 per cent in one.

II. The result of liver function test in simple goiter

Slight or moderate enlargement of the liver was noticed in 2 out of 7 patients. One patient with slightly enlarged liver had no sign of liver damage and the other one with moderately enlarged liver had signs of liver damages; result of half quantitative estimation of urobilinogen in the urine was 2 plus, T.T.T. was 5
units, C.C.F.T was 1 plus, cadmium reaction was R12. The later person was affected from hepatitis acuta several months ago. Other patients without liver enlargement had no sign of liver damage.

**III. The result of liver function test in myxedema**

Two patients with primary myxedema had liver enlargement and liver damage together. One patient has been suffering from myxedema for 10 years following a subtotal thyroidectomy and was treated with desiccated thyroid intermittently. The basal metabolic rate was $-19$ per cent. The liver edge was palpable 6 cm below the right costal margin. The liver surface was smooth, firm and not painful. The result of liver function test showed abnormality; half quantitative estimation of urobilinogen in the urine was 2 plus, cadmium reaction was R4, T.T.T. was 5 units, B.S.P. test was 5 to 10 per cent after 45 mins., C.C.F.T. was 2 plus.

Another patient with slightly enlarged liver has been suffering from primary myxedema for 5 years. In view of clinical laboratory test, it may be due to idiopathic origin. The basal metabolic rate was $-20$ per cent. The result of liver function test also showed abnormality; half quantitative estimation of urobilinogen in the urine was 1 plus, T.T.T. was 7 units, C.C.F.T. was 2 plus, cobalt reaction was R14, Gros reaction was 1 plus. The liver edge was palpable 2 cm below the costal margin, and the liver surface was smooth, firm and not painful. These functional impairment of the liver disappeared entirely after a duration of 4 months by the substitution therapy.

**DISCUSSION**

Many authors had reported the abnormal result of liver function test based on 1 to 2 liver function tests concerning the liver damage in hyperthyroidism (Kugelmann, 1930; Haines, Magrath and Power, 1941; Hurxthal, 1933). It should be considered that the liver has so many physiological actions that hepatic disability may have many, various and complicated aspects when causative factors are present. Therefore it is necessary to perform many liver function tests based on various metabolism and then to judge results synthetically.

In addition to the clinical course, clinical signs and laboratory tests, 12 liver function tests based on protein metabolism, pigment metabolism and excretory function were performed in order to discover which metabolism is more likely to be injured and which test is the most sensitive to detect it in various diseases of the thyroid gland.

In hyperthyroid patients, slight or moderate abnormal results of liver function tests were found in 75 per cent of patients and no abnormal result in 7 patients in whom the basal metabolic rate were altogether under 40 per cent. There has been considerable controversy about whether or not there is a proportionality between the degree of impairment of liver function and the increase of metabolic rate (Youmans and Warfield, 1926; Boyce and McFetridge, 1938; Schmidt, 1941).

According to the authors experiment, the number of abnormal liver function tests increases gradually as the basal metabolic rate increases. In view of basal
metabolic rate, these facts indicate that hepatic disabilities are hard to occur in patients in whom basal metabolic rates are under 40 per cent, and liable to occur above 40 per cent, and then there is some correlation between the number of abnormal liver function tests and the basal metabolic rates (Figure 1). Among 21 patients with liver damage, 14 patients had slight or moderate liver enlargement (67 per cent of 21 patients) and 7 patients had no liver enlargement. In these patients with liver enlargement, there was no previous history of liver disease and clinical signs of heart insufficiencies for instance auricular fibrillation and disturbance of myocard. One patient with slightly enlarged and soft liver had no sign of liver damage. Perhaps it may be due to the hepatoptosis.

Higgins (1933) found that livers of the rats fed thyroid increased in size and also in the extent of the restoration of the liver following partial surgical removal. Simons and Brandeis (1930) had noted a relative increase in the weight of the liver in thyrotoxic dogs. Bickel (1943) reported that moderate enlargement of the liver occurred in approximately 40 per cent of patients with hyperthyroidism. It may be considered that these striking occurrence of liver enlargement in comparison with normal are due to thyrotoxicosis but not due to the cardiac insufficiencies or other origins.

As the basal metabolic rate increases more than plus 30 per cent, the liver enlargement is more frequently found out. In regard to the interrelation between the grade of liver enlargement and the grade of basal metabolic rate, there is some relation in patients whose basal metabolic rate are under plus 60 per cent. On the contrary the grade of liver enlargement looks likely to decrease as the basal metabolic rate increases above 60 per cent (Figure 2). Then there seems to be a similar interrelation between the grade of liver enlargement and the number of abnormal liver function tests; as the later increases the former increases, but when the later increases beyond 6 the former seems conversely to decrease gradually (Figure 3). In respect to these disproportion, judging from the result of increasing abnormal liver function tests especially cobalt reaction, cadmium reaction, Takada—Jezler reaction, they may be due to the occurrence of cirrhotic phase.

Protein metabolism is more liable to be injured than other metabolism in hyperthyroid patients. Regarding the disturbance of protein metabolism, C.C.F.T., cobalt reaction and cadmium reaction seem to be the most sensitive tests in
hyperthyroidism with liver damage (Table 3). Subsequently T.T.T. seems to be sensitive.

It is said that C.C.F.T. test and T.T.T. are likely to be positive in diffuse form of the liver damage such as acute hepatitis and more certain phases of cirrhosis (Lichtman, 1953) and that cobalt reaction and cadmium reaction are more likely to be positive in cirrhosis.

In view of morbid anatomy, Haban, quoted by Bartels (1937), suggested the name “Cirrhosis Basedowiana” for the condition of liver found in fatal cases of toxic thyroid disease which showed chronic lesions of a cirrhotic type. Shaffer (1940) said that the lesion of great significance was chronic interstitial hepatitis in a study of 24 cases of hyperthyroidism.

According to the result of liver function tests based on the disturbance of protein metabolism and the state of liver surface, it is possible to say that hepatic disabilities noted in 21 patients of hyperthyroidism are connected with chronic lesions such as cirrhosis and chronic hepatitis.

Abnormal serum protein content is hard to occur, but in few cases unexplainable increase of serum protein content was noticed.

In relation to the disturbance of bile pigment metabolism, half quantitative estimation of urobilinogen in the urine was rather a sensitive test. All of the patients with abnormal urobilinogenuria had liver enlargement and abnormal result of liver function tests, so it may be possible to say that the measurement of urobilinogenuria is one of the most convenient and simple screening test for the hepatic disabilities in hyperthyroidism. Hyperbilirubinemia is rare and mild as it has been said.

Concerning the excretory function many authors reported the liver damages obtained by the utilization of bromsulphalein test in hyperthyroidism (Haines, Magrath, and Power, 1941; Maddock, Coller and Pedersen, 1941). According to the author's experiment, it is not a sensitive test to detect liver damage in comparison with another function tests (Table 3).

In simple goiter there was no detectable liver damage except one patient who was affected from hepatitis acuta several months ago. So it may be usual to find
no liver damage in simple goiter unless there are any complications.

Regarding the liver damage in myxedema, it is not yet precisely known how the hypothyroidism and the liver are related to each other functionally and why the hypothyroidism provokes the liver damage which is identical in the respects of liver function tests with those caused by hyperthyroidism.

According to the result of liver function test, it seems that generally there are liver damages which are detectable by the use of various liver function tests and curable by the hormone therapy in myxedema. Liver enlargement also seems to be a striking sign in myxedema as well as hyperthyroidism. The disturbance of protein metabolism is liable to occur and it is detectable by the utilization of C.C.F.T., cobalt reaction and cadmium reaction. The cause of liver damage in myxedema is not yet evident, but the mainspring of it may be due to hormonal disturbance as it occurs without another causes and is curable by the hormone therapy.

SUMMARY

By the use of various liver function tests, it was found that slight or moderate hepatic disabilities which seemed to be due to chronic lesions such as cirrhosis and chronic hepatitis was noticeable. In patients of hyperthyroidism hepatic disabilities were found 75 per cent and in patients of primary myxedema they were found in all of them and cured after successful treatment.

Hepatomegaly is the most striking sign of liver damage and shows a tendency to be related to the grade of basal metabolic rate in hyperthyroidism.

Half quantitative estimation of urobilinogen in the urine is the most convenient and simple screening test for hepatic disabilities in hyperthyroidism and myxedema.

Protein metabolism is more liable to be injured than other metabolism and cephalin cholesterol flocculation test, thymol turbidity test, cobalt reaction and cadmium reaction are most sensitive tests to detect it in hyperthyroidism and myxedema.

There is some relation between the grade of basal metabolic rates and the number of abnormal liver function tests; all the patients whose basal metabolic rates are below 30 per cent have no sign of liver damage and then as the basal metabolic rates increases the number of abnormal liver function tests increases the number of abnormal liver function tests increase gradually.

Hyperbilirubinemia is usually mild and rare as it has been said so.

Excretory function examined by utilization of bromsulphalein test is rather hard to be injured in hyperthyroidism.

In simple goiter, it seems to be the rule that there is no liver damage unless there are any complications.
REFERENCES