EVALUATION OF THE RELATIONSHIP BETWEEN
LONG-ACTING THYROID STIMULATOR, CLINICAL AND
BIOLOGICAL THYROTOXICOSIS AND EXOPHTHALMOS

By
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ABSTRACT

Long-Acting Thyroid Stimulator (LATS) determinations were performed on the unconcentrated serum of 92 hyperthyroid patients, using the slightly modified method of McKenzie. A positive LATS response was found in 27 per cent of patients with active thyrotoxicosis, in 55 per cent of patients with residual hyperthyroidism after 131 iodine therapy, in 63 per cent of patients with progressive exophthalmos and in 4 of the 4 patients with pretibial myxoedema. In active thyrotoxicosis, the incidence of LATS was the same in the untreated patients (26 %) as in the patients insufficiently treated with antithyroid drugs (27 %). In untreated and insufficiently treated patients, exophthalmos, LATS and thyroglobulin antibodies (TGA) were more frequently found in the younger patients. There was a quantitative correlation between the response to LATS and pretibial myxoedema. No relation was found between level of LATS and the severity of ocular signs in progressive exophthalmos or between level of LATS and the biological parameters of the thyroid function in active thyrotoxicosis: cholesterol, PB127I, 131I uptake tests and PB131I. In view of these data, it seems that the relationship of LATS to thyrotoxicosis and/or exophthalmos cannot be considered as a directly causal factor.

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The concept that clinical thyrotoxicosis may result from the loss of a normal relation between the hypothalamo-hypophysial system and the thyroid and thus from an excess of thyrotrophin (TSH) secretion is no longer accepted. The endogenous TSH secretion is on the contrary reduced, as shown by cytological observations of regressive changes in the pituitary (Wegelin 1926; Racadot et al. 1965; Murray & Ezrin 1966) and by the finding of low levels of serum TSH (Adams & Kennedy 1965; Lemarchand-Béraud et al. 1966; Bonyns 1967).

Several investigators have claimed that the long-acting thyroid stimulator (LATS), a gammaglobulin (Kriss et al. 1964; McKenzie 1965 a; Dorrington et al. 1965; Beall & Solomon 1966) elaborated outside the pituitary gland (Major & Munro 1962), may be the causal factor of thyrotoxicosis (Adams 1965; McKenzie 1965 b; Kriss et al. 1967) although definite evidence for this assumption is still lacking.

In the present study, the values of LATS have been measured in the serum of nearly one hundred thyrotoxic patients and an endeavour made to estimate the significance of the relationship of LATS to the clinical and biological signs of thyrotoxicosis and to exophthalmos.

PATIENTS

Ninety-two patients were studied. All had suffered previously from hyperthyroidism or were still hyperthyroid at the time of the examination. Nineteen patients had never been treated, 73 had been treated previously, with radioactive iodine (58), antithyroid drugs (11), or had undergone partial thyroidectomy (4). The thyrotoxicosis of the patients under antithyroid therapy was still in an active phase at the time of the examination. The antithyroid drugs had been discontinued for at least 3 weeks before the study. Among these patients, 40 were affected with progressive exophthalmos; in 4 of them, pretibial myxoedema appeared after treatment. No patients with thyrotoxicosis due to a solitary »toxic adenoma« were included. The diagnosis was established on the basis of the classical clinical and biological criteria (Means et al. 1963).

METHODS

1. Exophthalmos index. The degree of exophthalmos was estimated according to an arbitrary index ranging from 0 to 10 and based on the presence of the most frequent signs of eye involvement in thyrotoxicosis: burning, chemosis, proptosis, corneal injection, ocular paresis. Only cases with an index of 2 or more were considered.

2. Biological and immunological techniques. The methods for evaluating blood cholesterol, serum PB131I, six hours and twenty-four hours 131I uptake by the thyroid gland, plasma PB127I and thyroglobulin antibodies (TGA) have been described previously (Bastonie et al. 1965).

3. Serum LATS bioassay. Blood samples were drawn in the morning from fasting patients and immediately cooled to 4° C; during the next 2 days, the serum was
RESULTS

1. Relationship of LATS to clinical hyperthyroidism

Thirty hyperthyroid subjects were studied during active disease, 19 of whom were newly diagnosed untreated patients and 11 of whom had been insufficiently treated with antithyroid drugs. As indicated in Table 1, LATS was detected in 8 cases (27%), mean value for \( R \) 1.91, range 1.58 to 2.40. The incidence of the positive LATS response was the same in the untreated patients (26%) as in the patients treated with antithyroid drugs (27%). This is in contrast to the incidence observed in 18 patients still hyperthyroid after \( ^{131}I \) therapy (55%) and in 40 patients with progressive exophthalmos (63%). This last group included patients who had become normo- or hypothyroid after therapy. The mean value for \( R \) was about the same in all groups. In 4 cases of progressive exophthalmos with localised myxoedema, LATS was present at a strikingly higher level (mean \( R = 11.25 \)). As indicated in Table 2, the 30 untreated or insufficiently treated hyperthyroid patients were divided into 6 age groups of ten years each from 20 to 79. Exophthalmos and serum LATS were more frequent in the younger subjects. Four of the 8 LATS responses were detected in subjects in the third decade. In this group, severe eye signs were recorded in 3 out of 6 and TGA in 4 out of 6 cases.

2. Relationship of LATS to progressive exophthalmos

Although the LATS response was more frequently positive in thyrotoxic patients with progressive exophthalmos than in patients without exophthalmos (Table 1), the intensity of the reaction could not be related to the severity
Table 1.
Incidence of LATS response in thyrotoxicosis.

<table>
<thead>
<tr>
<th></th>
<th>No. of cases</th>
<th>LATS</th>
<th>%</th>
<th>Mean of »R« (20/2)</th>
<th>Range of »R«</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active hyperthyroidism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>without eye signs</td>
<td>24</td>
<td>2</td>
<td>8</td>
<td>1.92</td>
<td>1.82–2.01</td>
</tr>
<tr>
<td>with eye signs</td>
<td>6</td>
<td>6</td>
<td>100</td>
<td>1.90</td>
<td>1.58–2.40</td>
</tr>
<tr>
<td>all patients</td>
<td>30*</td>
<td>8</td>
<td>27</td>
<td>1.91</td>
<td>1.58–2.40</td>
</tr>
<tr>
<td>Residual hyperthyroidism (after ¹⁳¹I therapy)</td>
<td>18</td>
<td>10</td>
<td>55</td>
<td>2.26</td>
<td>1.56–4.14</td>
</tr>
<tr>
<td>Progressive exophthalmos</td>
<td>40**</td>
<td>25</td>
<td>63</td>
<td>2.12</td>
<td>1.56–3.80</td>
</tr>
<tr>
<td>Pretibial myxoedema</td>
<td>4**</td>
<td>4</td>
<td>100</td>
<td>11.25</td>
<td>1.75–38</td>
</tr>
</tbody>
</table>

* This group includes nineteen untreated patients with five positive LATS responses (26 %) and eleven patients, insufficiently treated with antithyroid drugs, with three positive LATS responses (27 %).

** This group includes patients with active and inactive thyrotoxicosis.

Table 2.
Incidence of active thyrotoxicosis, exophthalmos, LATS and TGA in relation to age (No. of cases).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>20–29</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
<th>60–69</th>
<th>70–79</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyrotoxicosis</td>
<td>6</td>
<td>4</td>
<td>9</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>30*</td>
</tr>
<tr>
<td>Exophthalmos</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>LATS</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>TGA</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>12</td>
</tr>
</tbody>
</table>

* These are the same patients as those presented in Table 1, line 3.

of the ocular signs (Fig. 1). This was true for untreated hyperthyroid subjects as well as for patients who had been treated with antithyroid drugs or radioiodine. Moreover 8 subjects with a positive LATS response had no ocular signs.

3. Relationship of LATS to biological hyperthyroidism

In active hyperthyroid patients no relation was observed between the LATS level and the main biological parameters of the thyroid function: blood...
Fig. 1.
Relationship of LATS to the index of severity of eye signs (50 cases).

Fig. 2.
Relationship of LATS to the blood cholesterol (43 cases).

cholesterol (Fig. 2). PB¹²⁷I (Fig. 3), ¹³¹I uptake tests (Fig. 4) and PB¹³¹I at the 24th h (Fig. 5) or even when only subjects with a positive LATS response were taken into account.
4. **Relationship of LATS to $^{131}$I treatment**

Thirty five patients, all with active hyperthyroidism but no eye signs, were considered as a whole. Amongst these, 11 had previously received $^{131}$I treatment between 1 month to 7 years before the LATS assay. The other 24 patients were newly diagnosed untreated patients. In the first group, the incidence of LATS was 5 times more frequent than in the second group as shown in Table 3. Moreover, amongst the 11 patients who had received radioiodine, LATS and progressive exophthalmos appeared after treatment in 2 cases.
Fig. 5.
Relationship of LATS to the PB$^{131}$I (27 cases).

Table 3.
Incidence of LATS in active thyrotoxicosis without eye signs in relation to $^{131}$I therapy.

<table>
<thead>
<tr>
<th>Thyrotoxicosis</th>
<th>No. of patients</th>
<th>Positive LATS response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>Treated with $^{131}$I</td>
<td>11</td>
<td>5</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The concept that LATS may be the causal factor of thyrotoxicosis is based on three series of data:

1. in most cases of neonatal hyperthyroidism, LATS has been detected in the serum of the newborn but has disappeared together with the clinical signs (Sunshine et al. 1965);

2. LATS is an active stimulator of the normal thyroid in experimental animals (McKenzie 1960; Pinchera et al. 1965) and in normal subjects (Arnaud et al. 1965);

3. a relationship between the values of LATS and certain biological parameters of thyroid function has been described by one group of investigators (Major & Munro 1962; Carneiro et al. 1966a).

It has also been suggested that the association between LATS and exoph-
thalamos observed by many investigators (Pimstone et al. 1963; Noguchi et al. 1964; Pinchera et al. 1965; Kriss et al. 1967) indicates some direct or indirect relationship (Kriss et al. 1967).

If the role of LATS in thyrotoxicosis or in exophthalmos were really a causal one, theoretically one should expect the following conditions:

1. a very high incidence of LATS in untreated thyrotoxicosis (and/or in progressive exophthalmos);
2. an increased level of LATS parallel to the severity of clinical and biological parameters of thyrotoxicosis (and/or to the severity of exophthalmos);
3. a reduced incidence of LATS in cured thyrotoxic patients (and/or after improvement of eye signs);
4. conversely, all patients with a LATS reaction should present thyrotoxic signs (and/or exophthalmos) and all patients without serum LATS should be in remission from thyrotoxic (exophthalmic) symptoms. The present observations as well as the data published in the literature are at variance with these theoretical postulations.

The incidence of LATS in 24 untreated or insufficiently treated thyrotoxic patients who were free from eye signs was only 8% (Tables 1 and 3) whereas in 30 untreated thyrotoxic patients including 6 patients with exophthalmos the incidence was 27% (Table 1). The same figure was found by Pinchera et al. (1965) and Kriss et al. (1967). While the peak of the age curve in our thyrotoxic cases was between 30–50 years and corresponded to the classic age distribution (Means et al. 1963), half of the patients with a positive LATS response were under 30 years of age (Table 2). LATS was more frequently detected in patients who had been submitted to $^{131}$I therapy between 1 month and 7 years before the LATS assay, but who were still thyrotoxic (Tables 1 and 3). This observation was already made by Pinchera et al. (1965), Kriss et al. (1967) and confirmed by Lipman et al. (1967) who observed an increase in the incidence of LATS in a prospective study before and after $^{131}$I therapy. This increased incidence cannot be related to a longer duration of the disease since in patients who relapsed after prolonged treatment with antithyroid drugs, the frequency of LATS was the same as in newly diagnosed cases (Table 1).

The absence of LATS in the serum of thyrotoxic patients has been related to the low sensitivity of the bioassay (Adams 1965). The incidence of LATS increased, however, when instead of total serum, concentrated gammaglobulins were used in the assay. By means of this refinement of the technique Carneiro et al. (1966 b) detected LATS in the serum of 85% of thyrotoxic patients whereas they only observed 60 to 70% in unconcentrated sera (Major & Munro 1962). It should be noted, however, that in the publication by Carneiro et al. (1966 b), the clinical criteria of the patients investigated were not specified. Hence, their results should probably be compared with the overall figure of 40 to 60% observed by several investigators (Noguchi et al. 1964; Basenjie et al.
1967; Lipman et al. 1967). Finally, Burke (1967) assumes that the absence of LATS from unconcentrated serum may be due to the presence of an albumin inhibitor in the serum. So far the existence of such an inhibitor has not been demonstrated and the question remains unanswered as to why the eventual serum inhibitor is active \textit{in vitro} and inactive \textit{in vivo}. These divergent data make one reluctant to admit that in active uncomplicated thyrotoxicosis, the low incidence of LATS is merely the result of an insufficiently sensitive method of detection.

The presence of LATS in subjects with no clinical signs of hyperthyroidism has been confirmed by several investigators (McKenzie 1961; Adams 1965; Pinchera et al. 1965; Lipman et al. 1967). This condition has been explained by the assumption that the thyroid parenchyma was unable to react: 1) because of thyroid destruction by the radioiodine therapy, 2) because of superimposed thyroiditis (McKenzie 1967). The explanation may hold for the cases treated with radioiodine but is doubtful in the cases in which thyroid antibodies have been detected. Indeed in a recent study from this department, in 50\% of the patients with active thyrotoxicosis the serum contained both LATS and TGA (Bastenie et al. 1967). It is now generally admitted that circulating thyroid antibodies reflect the presence of an auto-immune process within the thyroid gland: a relation between serological reactions and thyroiditis lesions in the thyroid has been demonstrated in thyrotoxicosis by Schade et al. (1960). In the present study, LATS and TGA had parallel incidence in untreated patients before the 3rd decade (Table 2). Thus, the presence in the thyroid of inflammatory lesions is not always an explanation for the absence of thyrotoxicosis. Finally, LATS has also been found in normal control subjects without any history of thyroid disease (McKenzie 1961; Adams 1965; Lipman et al. 1967; Bonyns, in press). These data are considered to be misleading (Adams 1965) because of the lack of specificity of the McKenzie assay.

Up to the present no investigator has shown a relationship between LATS level and the severity of the clinical signs of thyrotoxicosis. Major & Munro (1962) and Carneiro et al. (1966 a) have claimed that there is a relationship between LATS response and the radioactive turnover in the thyroid gland only when LATS positive subjects are considered. The present data as well as those of Pinchera et al. (1965) are in contrast with these findings. No relationship has been found between the value of LATS and all the classical parameters of thyrotoxicosis: cholesterol (Fig. 2), PB$^{131}$I (Fig. 3), $^{131}$I uptake at 6 and 24th hours (Fig. 4) and PB$^{131}$I (Fig. 5).

The remission in hyperthyroidism is not paralleled by changes in LATS response: 2 and 10 years after remission, respectively 27 and 10\% of the patients still presented positive LATS reaction in their serum (Lipman et al. 1967). Only in neonatal hyperthyroidism is there a definite relationship between disappearance of LATS and recovery from thyrotoxicosis. However, there is
obviously a fundamental difference between spontaneous hyperthyroidism and neonatal thyrotoxicosis.

The incidence of LATS in thyrotoxicosis with exophthalmos is definitely higher than in uncomplicated hyperthyroidism (Pinchera et al. 1965; Lipman et al. 1967). These data are confirmed in the present study (Tables 1 and 3) which also indicates a relationship between hyperthyroidism, eye signs and LATS in young untreated subjects (Table 2). However, thyrotoxic ophthalmopathy has been reported without any serum LATS (Werner et al. 1967). This was also the case in 15 out of 40 patients of the present study. Conversely the presence of LATS was not always accompanied by the development of eye signs (Fig. 1) and eye signs with positive serum LATS reaction are not always accompanied by thyrotoxicosis (Liddle et al. 1965; Hall et al. 1967). LATS has also been observed in one case of Hashimoto’s disease without hyperthyroidism and exophthalmos (Jayson et al. 1967), and in 4 out of 46 patients with asymptomatic atrophic thyroiditis (Bastenie et al. 1967).

On the other hand, our results indicate that the level of LATS expressed by »R« is independent of the presence of eye signs and when these were present, to their severity (Fig. 1) (Pinchera et al. 1965). However, when exophthalmos and LATS coexisted, the spontaneous disappearance of the eye signs was usually associated with disappearance of serum LATS (Lipman et al. 1967). Nevertheless after cortisone therapy, LATS completely disappeared while the eye signs only partially improved (Werner 1966; Bastenie et al. 1967; Lipman et al. 1967). The same observations have been made after total thyroidectomy (Catz 1967; Bonnyns & Demeester-Mirkine, unpublished).

In conclusion, the present investigations are in agreement with the results and conclusions of the very recent study of Lipman et al. (1967). In view of the clinical data indicated by these investigators and because of the biological data of the present study, it seems that the relationship between LATS and thyrotoxicosis appears as significant but cannot be considered as directly causal. The same seems to hold for the relationship between LATS and exophthalmos.

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