SEQUENTIAL STUDY OF THE IMPAIRMENT OF THYROID FUNCTION IN THE EARLY STAGE OF SUBACUTE THYROIDITIS

By
Daniel Glinoer, Nicole Puttemans, André J. Van Herle, Monique Camus and André M. Ermans

ABSTRACT
A sequential study of various parameters of thyroid metabolism has been carried out in 2 patients during the weeks following the clinical onset of subacute thyroiditis, the aim being to define the nature and extent of the anomalies of thyroid function. In the early stage, serum thyroxine, protein bound iodine and T3 resin uptake levels were in the thyrotoxic range. In both cases, the serum thyroxine values further decreased with a half-life of 7 days and reached the hypothyroid range at the 6-7th week. Both 131I uptake and TSH plasma levels were found to be low and concomitantly rose at the 6-7th week. In one patient the serum thyroglobulin level was strikingly elevated at the beginning and then fell fairly rapidly; however in both patients, the serum thyroglobulin values remained abnormal. The present study confirmed the concept of a sudden release of preformed hormone stores. Furthermore, the following points

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Address reprint requests to Dr. D. Glinoer at the Department of Radioisotopes; St. Peter’s Hospital, rue Haute 322, 1000 – Brussels, Belgium.
were evident: a) marked and transient release of thyroglobulin; b) interruption of the secretory activity during at least 7 weeks; c) adequate functioning of the pituitary-thyroid control mechanism and d) partial recovery of the thyroidal iodine uptake at a time when the hormone secretion was still undetectable.

The main feature of De Quervain's thyroiditis is the development of acute degenerative processes in the thyroid parenchyma, resulting in the breakdown of follicular structures (Bastenie et al. 1972). Large quantities of thyroid hormones and iodoproteins are suddenly released into the circulation (Ingbar & Freinkel 1958). Thyroid cell impairment further leads to temporary interruption of iodide concentrating processes and hormone synthesis (Greene 1971).

The sharp release of preformed intrathyroidal hormone stores can cause the sudden appearance of clinical signs of thyrotoxicosis, followed eventually by clinical and biological signs of thyroid insufficiency.

The role played by the thyroid stimulating hormone (TSH) in the course of the disease has not been elucidated. According to some investigators the levels of TSH are found to be normal in the initial phase of the disease though others maintain that they are low or even high (Lemarchand-Béraud et al. 1969). Some investigators hold that the administration of exogenous TSH cannot reestablish the iodine uptake by the gland (Skillern et al. 1956; Mc Jefferies et al. 1956), while others report partial resumption of the process in certain cases (Robbins et al. 1951; Lamberg et al. 1960). The present report is a follow-up study of the various parameters of thyroid activity during the weeks following the onset of subacute thyroiditis.

The purpose of this study was to try to define the nature and extent of the anomalies occurring in the parameters of thyroid function during the course of the disease, and the role played by the pituitary-thyroid feedback mechanism. We studied 2 cases of severe thyroiditis. The patients were treated exclusively with prednisone during the initial phase of the disease. The various parameters studied were the level of serum thyroxine (T₄I), the level of serum thyrotrophin (TSH), T₃ resin uptake (RT₃U), the level of serum thyroglobulin (HTg) and the thyroidal uptake of ¹³¹I (UT). Furthermore tests reflecting inflammatory activity were performed.

**STUDY SUBJECT AND METHODS**

**Patients**

*Case No. 1 – F. R.* – This 43 year old female, with no personal or familial history of thyroid disease was admitted to the hospital complaining of fever (38°C), bilateral neck tenderness radiating to the ears and dysphagia. Her complaints started 3 weeks before admission. The following symptoms reflecting clinical thyrotoxicosis were
present: perspiration, nervousness, palpitations, diarrhoea, weight loss, asthenia and tachycardia (112/min).

The skin was warm and moist. The thyroid gland was enlarged, firm, mobile and tender on palpation. Four days after admission prednisone (20 mg q. d.) was started. Rapid improvement was noted and the medication was continued for 1 month. At this point, clinical signs of failing thyroid function were apparent, and substitution therapy with L-T₃ (10 and later 20 µg q. d.) and L-T₄ (50 and later 100 µg q. d.) was started. Three months later the thyroid gland was barely enlarged, multinodular and non tender on palpation.

The patient was taking oral contraceptives (lynestrol 2.5 mg and mestranol 0.075 mg q. d.).

Case No. 2 – J. S. – A 47 year old female, with no personal or family history of thyroid disorders developed pharyngitis with dysphagia and fever at the beginning of May 1972. Two weeks later she noted swelling of the right thyroid lobe followed by involvement of the left lobe. Severe neck pain was present. When the patient was first admitted to the hospital clear signs of thyrotoxicosis were noted, e.g., profuse diaphoresis, nervousness, weight loss (2 kg), frequent palpitations, insomnia, severe asthenia, fever (38.2°C), tachycardia (100/min), warm and moist skin, and tremor of the extremities. The thyroid was diffusely enlarged, very firm and extremely tender on palpation. Cervical adenopathy was absent.

Treatment with prednisone (20 mg q. d.) was started immediately, and continued for 12 weeks. Rapid improvement was observed, but definite signs of hypothyroidism appeared after 5 weeks. Substitution therapy was started consisting of a combination of L-T₃ (20 µg q. d.) and L-T₄ (100 µg q. d.) and this was continued for more than 3 months. Thyroid palpation then revealed a normal thyroid gland.

Methods

Plasma protein iodine (PB¹²⁷I) was determined by the technique of Barker et al. (1951), adapted for the autoanalyzer Technicon (Technicon Instrument Corporation, Chauncey, New York). Normal values range from 4.0 to 8.0 µg/100 ml.

Serum thyroxine (T₄I) was determined by the method of Murphy et al. (1966). Results are expressed in terms of thyroxine iodine. The normal range is 3.5 to 7.5 µg T₄I/100 ml.

A T₃ resin uptake test (RT₃U) was performed with the Thyopac 3 kit (Radiochemical Center, Amersham, England) using the technique described by Clark & Brown (1970). Results are expressed in per cent of the values obtained in a control serum pool.

The normal range is 94 to 118% (hypothyroidism 118% or more and hyperthyroidism 94% or less).

Thyroid stimulating hormone (TSH) was measured by radioimmunoassay Odell et al. (1967). The normal level is less than 10 µU/ml. The normal mean detectable value is 5.2 µU/ml.

The serum thyroglobulin (HTg) was measured by a double antibody radioimmunnoassay recently developed by Van Herle et al. (1973). The normal mean detectable levels in the female are 6.0 ng/ml (range 1.6 to 20.7 ng/ml).

Antithyroglobulin antibodies (ATA) were measured according to the method of Boyd (1951). Sera from both patients studied did not contain HTg autoantibodies.

Uptake of radioiodine (UT) was determined 24 h after oral administration of 3 µCi carrier free ¹³¹I. Average normal values for our laboratory are 35 to 55% Camus et al. (1968).
RESULTS

1. Initial biological results

In both cases the first sera for analysis were obtained 3 (case No. 1) (Fig. 1) or 2 weeks (case No. 2) (Fig. 2) after the onset of the clinical symptomatology.

In both instances the uptake of radiiodine was initially non-existent. Levels of $T_1$ and $T_3$ resin uptake were characteristic of severe thyrotoxicosis. Similar abnormalities were noted for the PBI, initial values being respectively 12.7 (case No. 1) and 13.7 (case No. 2) $\mu$g/100 ml.

Patient J. S. (case No. 2) had an elevated serum thyroglobulin level when first tested, i.e. about 50 times the upper limit of normal. In case No. 1 in which the investigation started later, the level of HTg was just above the normal range. The level of TSH was low in both patients right from the

![Fig. 1.
Patient F. R. (case No. 1). Evolution of parameters of thyroid function during acute phase of De Quervain’s thyroiditis. Shaded areas correspond to the normal range.](image-url)
Patient J. S. (case No. 2). Evolution of parameters of thyroid function during acute phase of De Quervain's thyroiditis. Shaded areas correspond to the normal range.

beginning of the observations. An increased sedimentation rate, fibrinogen and \( \alpha_2 \)-globulin levels reflected the inflammatory process. In case No. 2 a moderately elevated leucocyte count was also noted.

2. Evolution under prednisone treatment

Changes in test reflecting the inflammatory process under the influence of prednisone treatment (20 mg q. d.) are shown in Table 1. The various parameters gradually normalized although more slowly in case No. 2. Figs. 1 and 2 show the striking similarity with regard to changes in thyroid function that occurred in both patients.

First there was a gradual decrease in the levels of thyroxine iodine until about 20–30 days after the start of the investigations; when the \( T_4 I \) levels
Table 1.
Test results reflecting inflammatory process in subacute thyroiditis in patients F. R. and J. S.

<table>
<thead>
<tr>
<th>Case No. 1 F. R.</th>
<th>Day 1</th>
<th>Day 10</th>
<th>Day 20</th>
<th>Day 30</th>
<th>Day 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte sedimentation rate (N ≤ 10 mm/H)</td>
<td>55</td>
<td>15</td>
<td>10</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Fibrinogen (N ≤ 350 mg/100 ml)</td>
<td>545</td>
<td>350</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum proteins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\alpha_2$-globulins (N: 8–13 %)</td>
<td>12.5</td>
<td>9.4</td>
<td>12.3</td>
<td>10.4</td>
<td></td>
</tr>
<tr>
<td>$\gamma$-globulins (N: 15–25 %)</td>
<td>19.0</td>
<td>14.6</td>
<td>15</td>
<td>15.8</td>
<td></td>
</tr>
<tr>
<td>Leucocytes (N ≤ 9000/mm³)</td>
<td>5500</td>
<td>8300</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case No. 2 J. S.</th>
<th>Erythrocyte sedimentation rate</th>
<th>127</th>
<th>105</th>
<th>35</th>
<th>22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>1352</td>
<td>675</td>
<td>350</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum proteins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\alpha$-globulins</td>
<td></td>
<td>21.5</td>
<td>17.8</td>
<td>15.8</td>
<td></td>
</tr>
<tr>
<td>$\gamma$-globulins</td>
<td></td>
<td>20.6</td>
<td>20.7</td>
<td>18.3</td>
<td></td>
</tr>
<tr>
<td>Leucocytes</td>
<td>11 200</td>
<td>7000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 3.
Half-life of $T_4$ in patients F. R. and J. S. during the early observation period of subacute thyroiditis. Dotted line corresponds to 7 days theoretical half-life of thyroxine.
were as low as 0.1 (case No. 1) and 1.2 (case No. 2) μg/100 ml. The levels of plasma PB\textsuperscript{131}I (not shown in Figs. 1 and 2) followed a similar pattern. The increase in the T\textsubscript{3} resin uptake was a mirror image of the decrease of T\textsubscript{4}I; the results first indicated values typical of thyrotoxicosis and gradually fell to values in the hypothyroid range. When T\textsubscript{4}I levels were plotted on a semilog scale as functions of time (Fig. 3), a fall occurred according to a linear function. The disappearance rate was similar in both patients and was almost identical to the disappearance rate of thyroxine, calculated on the basis of half-life of 7 days. The extremely elevated level of serum HTg in case No. 2 fell very rapidly. The levels of TSH remained low until about the 20th day and then rose sharply. This pituitary TSH release was triggered when the serum thyroxine levels reached definite hypothyroid levels. The uptake of radioiodine remained extremely low until the TSH levels rose. Finally in both cases, thyroid stimulation under the influence of TSH was accompanied by a new increase in the level of serum HTg.

3. Evolution under treatment with thyroid hormones

The administration of a combined preparation of thyroxine (100 μg/day) and triiodothyronine (20 μg/day)\textsuperscript{1} gradually restored the values of T\textsubscript{4}I, RT\textsubscript{3}U and PB\textsuperscript{131}I to normal. The TSH stimulation continued in case No. 1 during the first few days when small doses of T\textsubscript{4} and T\textsubscript{3} were administered. It declined as soon as higher doses were given. In case No. 2 the substitution therapy also caused a fall in the uptake of \textsuperscript{131}I.

\textbf{DISCUSSION}

The laboratory results obtained in the 2 patients respectively 3 weeks (case No. 1) and 2 weeks (case No. 2) after the clinical onset of subacute thyroiditis, reflect severe thyrotoxicosis although uptake of radioiodine is completely absent (Lamberg \textit{et al.} 1960; Perloff 1956). This confirms the concept of the sudden release of preformed thyroid hormone stores in the circulation, reported previously (Ingbar & Freinkel 1958). Our data indicate that the phenomenon is associated with extremely high serum thyroglobulin levels which fall fairly rapidly (case No. 2). However, the serum HTg level is only moderately increased above the normal range at the third week in case No. 1, where a rapid disappearance of plasma HTg probably accounts for the moderately elevated levels found in this case at the start of the study (Dorta & Béraud 1961; Stemmerman & Hilo 1956). The present findings are in conflict with the observations of Torrigiani \textit{et al.} (1969) who reported normal HTg levels in subacute thyroid-

\textsuperscript{1} Novothyral\textsuperscript{®}, Merck.
itis. Indeed in our 2 subjects the values of serum HTg remained definitely abnormal throughout the period of observation and rose significantly when the secretion of endogenous TSH was resumed. This is not surprising since increments in HTg levels following exogenous TSH administration or endogenous TRH mediated TSH release have been reported recently by Uller et al. (1973).

The fall in plasma T₄I levels is exponential during the first weeks. The single exponential decay strongly suggests that the T₄I levels actually reflect the peripheral catabolism of the initially discharged hormonal iodine and is consistent with the view that no appreciable hormone secretion occurred in both patients during this initial period of observation (7 weeks). It is of interest that the period of this exponential process is very close to the 7 days half-life of thyroxine in euthyroid subjects although in our observations, both patients were successively hyperthyroid, euthyroid and hypothyroid.

In support of the interruption of thyroid activity is also the complete absence of radioiodine uptake until about the 6th week (Völpé et al. 1958) after the onset of the symptoms. These findings strongly suggest a complete blocking of the various stages of intrathyroidal metabolism in these patients during the initial phase of their disease. The only restriction to this interruption is the lack of data concerning the evolution of the plasma triiodothyronine levels. It is interest that the resumption of activity of the iodide pump coincides with a rise in the levels of endogenous TSH indicating that at this point the lack of uptake is at least partly related to the absence of TSH stimulation (Weinstein et al. 1967). The fact reported by various investigators that the resumption of uptake of ¹³¹I after exogenous TSH injection is absent or partial during the first weeks of the disease is well documented and indicates that the impairment of the thyroid cell remains a crucial factor in the disturbance of the iodide concentrating mechanism (Dorta & Béraud 1961). It is of importance to note that in case No. 2 the spontaneous recovery of radioiodine uptake is achieved even though the level of thyroxine iodine continues to fall. This suggests a time lag between the re-establishment of the iodide concentrating process in the thyroid and the resumption of the mechanism of hormonal synthesis and secretion. The need for substitution therapy prevented us from observing the time sequence followed by the thyroid gland in the resumption of thyroid hormone synthesis.

The inverse relationship between TSH levels and T₄I levels throughout the course of the disease implies an intact pituitary-thyroid feedback mechanism. As expected a pituitary response is elicited only when T₄ iodine levels fall to the hypothyroid range. It has been shown that large doses of glucocorticoids could partly suppress TSH secretion (Wilber & Utiger 1969; Nicoloff et al. 1970). The question thus arises as to the interference of prednisone treatment on the evolution of the TSH levels reported in our patients. Therefore it must
thus be pointed out that the rebound of plasma TSH levels occurred in case No. 2 without any modification of the corticoid treatment and in case No. 1 just before the prednisone administration was withdrawn.

In conclusion, the study of 2 cases of severe subacute thyroiditis confirms the concept of a sudden release into the circulation of preformed thyroid hormone stores and supplies evidence for the interruption of hormonal secretion during about 2 months.

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REFERENCES


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