Can stress induce dysimmune dysthyroidism?

Le stress peut-il induire des dysthyroïdies dysimmunitaires ?

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Abstract

Hyperthyroidism due to Graves’ disease is autoimmune in origin. The initiation of dysimmunity responsible for the disease is still poorly understood. Numerous population studies show that genetic factors have a major role, but the environment and any kind of stress also contribute to the onset of the disease. There remains the recurring question for medical experts of the accountability of stress in the onset of Graves’ disease. To date, it is impossible to establish a direct link between this disease and a specific stress. The relationship can only be hypothetical, indirect and partial.

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Résumé

L’hyperthyroïdie due à la maladie de Graves-Basedow est d’origine auto-immune. L’initiation de la dysimmunité responsable de la maladie est toujours mal connue. Les nombreuses études de populations montrent que les facteurs génétiques ont un rôle prédominant, mais l’environnement participe également au déclenchement de cette maladie, et parmi eux les stress de toute nature. D’où la question récurrente, en expertise médicale, de l’imputabilité d’un stress dans la survenue d’une maladie de Graves-Basedow. À ce jour, il est impossible d’établir un lien direct entre cette maladie et un stress spécifique. La relation ne peut être qu’hypothétique, indirecte et partielle.

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Dysimmune dysthyroidism is a collection of autoimmune pathogenic thyroid diseases affecting 5% of the general population with an 80% female predominance. There are significant variations within several population groups, which may be explained by the pathogenesis of these autoimmune diseases. Autoimmune thyroid dysfunction results either as chronic lymphocytic Hashimoto’s thyroiditis or its clinical variants (post-partum, adolescent and silent thyroiditis) and as Graves-Basedow disease [1], lymphocytic infiltration of the thyroid gland and the presence of circulating auto-antibodies bear witness to these antigen specific thyroid abnormalities which are specific to dysimmune diseases. Dysimmune thyroiditis evolves towards hypothyroidism over a long-term period and can take several months or, more often, several years. Graves-Basedow disease characteristically has a rapid and progressive evolution over a few weeks or months to hyperthyroidism. It is because of this narrow time frame, between Graves-Basedow disease onset and a physical or psychic stress that a cause-and-effect relationship could be evoked [2]. Conversely, it is difficult to relate the development of chronic thyroiditis to a specific non-iatrogenic environmental event, such as stress, given the long lag time between the initial stage of the disease and its clinical expression.

If stress contributes to the onset of Graves-Basedow disease, then medico-legal implications and reimbursement could come into play.

Our intent is to report today knowledge of thyroid’s dysimmune pathogenesis dysfunction with a particular focus on Graves-Basedow disease. We will discuss stress’ possible role in the onset or progression of the disease and if there is clinical or epidemiological evidence proving or disproving a relationship between stress and the disease onset.

1. Patho-physiology of dysimmune thyroid dysfunction

This patho-physiology dysfunction is the result of an autoimmune disease directed against thyrocytes, that is, thyroid follicular cell elements which constitute the essential functional
unit secreting thyroid hormones (thyroxin/T4 and Triiodothyronine/T3) from thyroglobulin (Tg) [1,3].

The initial factors for autoimmunity impaired function remain poorly understood. There is a tissue and humoral reaction linked to the abnormal presentation of antigens specific to the thyroid (thyroid peroxidase, thyroglobulin, and TSH receptors). This induces, among other things, a production of antiperoxidase antibodies, anti-thyroglobulin (characteristic of Hashimoto’s disease) and TSH anti-receptors antibodies (for Graves-Basedow disease). In Hashimoto’s disease, autoimmune damage causes destruction of the thyroid vessels. This mechanism of cell destruction involves all immunocytes, with preference towards a cellular response involving, among others, Th1 and Th2 lymphocytes.

In Graves-Basedow disease, the TSH anti-receptors antibodies (immunoglobulin G) initially stimulate this receptor and thus is responsible for hyperthyroidism pathology may cause long-term destruction of thyocytes such as in Hashimoto’s thyroiditis.

There are multiple and poorly understood etiological causative factors of dysimmune thyroid dysfunction [4], with a clear predominance of genetic factors over environmental impact. Population studies show a predisposition to these diseases in the presence of major histocompatibility genes HLA A1 B8 and DR3 in Caucasians, and HLA B35 DRw12 in the Japanese. Studies of identical twins enabled us to evaluate an approximate 75% genetic impact for predisposition of dysimmune thyroid dysfunction. It was not, however, possible to identify the responsible genes [5–7].

Environmental factors therefore represent 25% of other etiologies: iodine intake, viral and microbial infections, smoking, selenium deficiency, and low birth weight [8]. Somatic and/or psychological stress, whether acute or chronic, are also part of essential putative etiological factors in the onset of Graves-Basedow disease [9–12]. In 1825, ten years before the disease’s description by Graves [13] and Basedow [14], Parry [15] described clinical signs of hyperthyroidism appearing in a 21-year-old woman which occurred shortly after an emotional stress associated with a non-injurious fall from her wheelchair. For over a century, many studies have tried to establish a relationship between the onset of Graves-Basedow disease and stress. Assuming that this relationship exists, the only available pathophysiological explanation is that the activation of the hypothalamic-pituitary ACTH function by acute or chronic stress, inducing alternating hyper and normal glucocorticoid function, is itself responsible for a loss of immunological balance [16–18]. A recent study suggested that the down-regulation of glucocorticoid function could be due to an endotoxin-induced immune response [19]. However, mechanisms of activation of thyroid immunity are complex and remain incompletely known.

2. Stress and thyroid: epidemiological and case-control studies

While many studies support a relationship between the occurrence of stress and the onset of a Graves-Basedow disease, there exist a lesser number of studies that do not support this relationship. The majority of studies are marred by numerous methodological flaws, making them unusable. These flaws include: too small a sample, lack of a control population, non-discrimination between the various etiologies of hyperthyroidism, and inaccuracy in the study of stressful circumstances.

Epidemiological studies focusing on populations subjected to acute and chronic stress over long periods, such as war and occupation, report a significant increase in the incidence of Graves-Basedow disease during or immediately following the event [20]. This is true for the war of 1935–1940 in France and for the people of Copenhagen and Brussels [21] during the same period. On one hand, the problem with these studies is the lack of discrimination between the hyperthyroidism of Graves-Basedow disease and other causes of hyperthyroidism. On the other hand, there is no consideration of other environmental factors such as nutrition, iodine intake, infection, smoking, etc. During a recent study in Yugoslavia, Paunkovic [22] found a relative risk factor of 5 connected to the conflict between 1992 and 1995. However, Hadden’s epidemiological study conducted in Ireland [23] in the period of conflict between 1969 and 1971, did not find an increase in the incidence of Graves-Basedow disease over the 1966 and 1968 previous conflict period. It is possible that the differences recorded for the “stress effect” is variable from one population to another due to differences in these populations’ genetic impact: the stress effect is all the more important if genetic impact is low.

While case-control studies are few, they remain the only ones available to use. These studies help to better isolate the specific role of stressful circumstances concerning the onset of Graves-Basedow disease.

The Table 1 summarizes the most relevant recent studies [24–33].

The relative risk associated with any kind of emotional stress is shown as zero to 7.7 times in the Yoshuichi study [29]. The most interesting and recent study was reported by Effraimidis et al. [33]: this prospective study analysed the outcome of 790 euthyroid women in terms of thyroid dysimmunity, in correlation with stressful events. After 5 years follow-up, the authors showed that there was no relation between hyper/hypothyroidism and stressful life events.

3. Conclusion: can Graves-Basedow disease be attributed to stress?

Even if the bulk of studies show a relative risk increase of Graves-Basedow disease after a psychological trauma or stress, it is impossible to formally establish a relationship of direct cause-and-effect between the two. Indeed, these studies emphasize an association with genetic or environmental predisposing factors. It is difficult however to challenge an ancient custom of recognizing post-traumatic Graves-Basedow disease. On one hand there is nothing in the scientific data to formally deny this; on the other hand official texts leave such an eventuality wide open.

In France, the Code of Social Security’s Appendix 14.3 on thyroid disease [34,35] states:
Table 1
Case-control studies for stress and Graves-Basedow disease.

<table>
<thead>
<tr>
<th>Authors/year (Ref)</th>
<th>Methodology</th>
<th>Delay between stress and hyperthyroidism</th>
<th>Population</th>
<th>Stress-related hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray, 1985 [24]</td>
<td>Interview/retrospective</td>
<td>6 months</td>
<td>50</td>
<td>No</td>
</tr>
<tr>
<td>Winsa, 1991 [25]</td>
<td>Questionnaire/retrospective</td>
<td>1 year</td>
<td>208</td>
<td>Yes</td>
</tr>
<tr>
<td>Sonino, 1993 [26]</td>
<td>Interview/retrospective</td>
<td>1 year</td>
<td>70</td>
<td>Yes</td>
</tr>
<tr>
<td>Kung, 1995 [27]</td>
<td>Questionnaire/retrospective</td>
<td>1 year</td>
<td>95</td>
<td>Yes</td>
</tr>
<tr>
<td>Radosavljevic, 1996 [28]</td>
<td>Interview/retrospective</td>
<td>1 year</td>
<td>100</td>
<td>Yes</td>
</tr>
<tr>
<td>Yoshiuchi, 1998 [29]</td>
<td>Questionnaire/retrospective</td>
<td>1 year</td>
<td>228</td>
<td>Yes</td>
</tr>
<tr>
<td>Chiovato, 1998 [30]</td>
<td>Prospective</td>
<td>1–30 years</td>
<td>87</td>
<td>No</td>
</tr>
<tr>
<td>Matos-Santos, 2001 [31]</td>
<td>Interview/retrospective</td>
<td>1 year</td>
<td>31</td>
<td>Yes</td>
</tr>
<tr>
<td>Topcu, 2012 [32]</td>
<td>Interview/retrospective</td>
<td>1 year</td>
<td>45</td>
<td>Yes</td>
</tr>
<tr>
<td>Effraimidis, 2012 [33]</td>
<td>Questionnaire/prospective</td>
<td>Follow-up 5 years</td>
<td>790</td>
<td>No</td>
</tr>
</tbody>
</table>

“The relationship of Basedow disease with trauma is generally accepted. In most cases the accident plays a trigger role on predisposed grounds. The syndrome appears almost immediately and usually within a few weeks. Beyond two months, the relationship can no longer be asserted.”

The above provisions do not keep to the period of one year as described in the majority of case studies. They concern only Graves-Basedow disease and are not linked in the larger sense to post-traumatic stress, nor do they provide a set level of accountability. These recommendations, although modified in 1993, actually date back much longer since on the “criteria for assessing disability” the basic metabolism and Achilles’ reflex time still appear without any reference to the biological methods developed since the 1980’s.

When Graves’ disease is diagnosed after an emotional stress caused by a third party, a medical expert should be able to clearly answer the two main questions typically asked for this type of application:

- is Graves-Basedow disease attributable to the stress?
- if yes, in what proportion?

Studies of population groups and of homozygote twins find that genetic factors account for 75% of Graves-Basedow disease. Many environmental factors, including stress, are only involved 25% of the time. One might be tempted to answer yes to the first question, with a maximum proportion of 25% to the second question. Such a response suggests that we first establish the patient’s genetic environment to determine if his population group is at risk. From that point, the percentage could be adjusted, which is impossible with the current data.

So, insofar as the link between stress and Graves-Basedow disease can only be “hypothetical due to conflicting data, or indirect (inserted into a pathogenic chain) and partial (it participates in the same way as other factors)”, it seems difficult to be affirmative, as physicians specializing in personal injury care ought to be.

Although there is no scientific proof linking Graves-Basedow disease to post-traumatic stress, can medical expertise discern it as a “benefit of the doubt”? Current practice tries to avoid a “lost chance” for the victim, but we must recognize this can also be quite unfair towards the party responsible for the trauma.

Disclosure of interest

The authors have not supplied their declaration of conflict of interest.

References

[34] Code de la sécurité sociale–Annexe I à l’art. R 434-32.