Stress and Depression in Graves’ Disease

Botelho, N.¹, Lipp, M.E.N.², Manso, P.G.³, Furlanetto, R.⁴, Abreu, M.T.⁵

¹PhD, Psychologist
Department of Ophthalmology,
Universidade Federal de São Paulo, Brazil.

²PhD, Psychologist
Instituto de Psicologia e Controle do Stress, Campinas, Brazil.

³MD, Department of Ophthalmology,
Universidade Federal de São Paulo, Brazil.

⁴MD, Department of Endocrinology,
Universidade Federal de São Paulo, Brazil.

⁵MD, Department of Ophthalmology,
Universidade Federal de São Paulo, Brazil.

ABSTRACT

To evaluate the incidence of stress and depression in Graves’ disease, given the presence or absence of exophthalmos and its relation to gender and age, in adults attending a free university healthcare service in Sao Paulo, Brazil. This was a cohort study. Adult individuals with a diagnosis of Graves' disease were studied, from both genders, divided into two groups according to the presence or absence of exophthalmos. Beck Depression Inventory and the Lipp Inventory of Stress Symptoms for Adults were administered to both groups when they were in thyrotoxicosis (compensated or in hyperthyroidism). A total of 82 individuals were studied of which 55 with exophthalmos while 27 was without exophthalmos. Frequency of stress and depression was not significantly different between groups ($X^2_{calc}=0.251; \ p=0.308$) and this result was not related to gender and age. However, when comparing the concomitance of stress and depression with gender, a significant increase was found in the frequency of symptoms in women with exophthalmos ($MacNemar \ Test \ p=0.033^*$), but this was not related to age. The presence of exophthalmos in Graves’ Disease contributed to the coexistence of stress and depression in women, but not in men.

Keywords: Graves’ disease, Exophthalmos, Psychological Stress, Depression, Psychological tests.

Introduction

Graves’ Disease affects 0.5% of the Brazilian population (Abreu et al., 1994), its incidence being greater in women (a ratio of 6:1 to men) with a greater prevalence during the 3rd and 4th decades (Barrie, 1993; Gorman, 1983), similar to the results found in the United States and the North of England (Char, 1997). The etiology of Graves’ Disease is an autoimmune organ-specific disease characterized by the presence of antibodies that stimulate the thyroid gland (Volpe, 1985) and since it is considered to be an autoimmune disease, one might expect stress to play an important role in the onset of the disease in genetically predisposed individuals and, moreover, psychological changes due to emotional stress might be closely associated with the onset of hyperthyroidism (Chiovato & Pinchera, 1996). Environmental and emotional components might be a factor, not only in the onset of symptoms but also in their aggravation (Pinho Junior, 2003). Thyrotoxicosis can cause psychological disturbances and changes in behavior such as anxiety or emotional passivity that may compromise the way people cope with life events, being a consequence of and not a contribution to the disease (Stern et al., 1996). However, the evidence of contribution of stressful life events to the development and prognosis of the disease is circumstantial and stress-related studies still hold many methodological limitations and the biological mechanism by which stress affects the disease is still unclear (Mizokami et al., 2004).

Since Salve (1952) described his theory on the adaptation syndrome, others have investigated the concept of stress and its role in many clinical manifestations. In Brazil, Lipp (2004) introduced the concept of stress as a psychophysiologic reaction of the human organism, which has a need to deal with something that threatens its homeostasis. It could be an attempt to surmount a challenge, to overcome a threat or deal with the need to adapt to a specific moment, good or bad. At this moment a biochemical process is established (Lipp & Malagris, 2001; Lipp, 2003), and a hormonal mobilization occurs to enhance the organism and enable it to react properly to the stress. When this does not happen, the organism cannot resist the threat and starts to manifest symptoms (Selye, 1984) which modify neurotransmitters, hormones and cytokine patterns and alter the immune system, which leaves the organism...
vulnerable to many clinical conditions (Lipp, 2004), particular
to the genetic predisposition of each individual.

Women seem to be more vulnerable to autoimmune diseases
because stress can disturb the flow of sexual hormones and
send inadequate messages to the cells of the immune system,
which could attack the tissue in their own bodies and have
adverse consequences (Tanganelli, 2004). Age also contributes
to different reactions to stressful life events. Women are once
again more vulnerable the more sexually, professionally and
socially active they are because of the demands from family and
from social and cultural life, which increases when there is no
physical or emotional support and contributes to the
manifestation of the symptoms.

Depression can also be triggered by a general medical condition
as a consequence of a specific condition. General medical
scenarios are frequently associated with mood changes in
neurological conditions, metabolic, endocrine, self-immune,
and this difference is attributed to the impact of sexual
malignancies, viral infections, amongst others. Studies have shown that
depressive episodes occur twice as much in women than in men,
with symptoms varying greatly. North American data point to
a prevalence of depression of 21% in women and 13% in men
and this difference is attributed to the impact of sexual
hormones on the emotions, especially during the reproductive
stages of life (APA, 2000; Soares et al., 2001).

Study Objectives

The objective of this study was to evaluate patients with Graves’
Disease with regard to the presence of stress and depression
taking into consideration the presence or absence of
exophthalmos, and its relation to gender and age. Exophthalmos
was the selected variable due to the aesthetic aspect, often
involving disfiguring that could contribute to the presence of
both symptoms.

The study was approved by the Ethics Committee of
Universidade Federal de São Paulo under the number 0680/02.

Materials and Methods

Design: This was a cohort study.

Instruments: Beck Depression Inventory - BDI (Beck & Steer,
1993b) and Lipp Inventory of Stress Symptoms for Adults
(LISS) (Lipp, 2000). The BDI had already been translated and
validated for the Brazilian population (Cunha, 2001) and the
LISS is a Brazilian instrument used to measure stress (Lipp,
2000).

Procedures: (1). All participants signed a consent form after the
diagnosis of Graves’ disease and the measurement of
exophthalmos. (2) A trained medical doctor was able to
diagnose the disease by means of blood examinations, the
duration of the disease and the measurement of exophthalmos.
(3) The Beck Depression Inventory (BDI) (Cunha, 2001) and
the Lipp Inventory of Stress Symptoms for Adults (LISS) (Lipp,
2000) were administered by a trained psychologist. (4) The
statistical procedures included the Chi-Squared test for possible
associations, the Fisher’s Exact test for associations, the
McNemar test to analyze concomitance of symptoms and the
Mann-Whitney test to calculate how homogeneous groups
were related to age. All statistical tests were carried out by
a computer based software, the Statistical Package for Social
Sciences - SPSS - for Windows version 7. The BDI (Beck &
Steer, 1993b; Cunha, 2001) consists of an inventory of 21
items, each having four possible answers, similar to a
Lickert-Scale for different severity of depression. The items
are sadness, pessimism, feeling of failure, dissatisfaction,
guilt, punishment, self-repulsion, self-criticism, suicidal
thinking, crying, anger, social isolation, indecision, changes
toward self-image, difficulty in working, insomnia, tiredness,
loss of appetite, weight loss, somatic worries and reduced
libido. Individuals are asked to choose the best option about
how he/she feels about the last week, including ‘today’. The
LISS (Lipp, 2000) is used in diagnosing the presence or
absence of symptoms of stress. When individuals have
stress, the instrument is able to identify how stress
manifestation occurs more frequently, through physical or
emotional symptoms. A list of symptoms is presented to the
individual, referring to the last 24 hours, one week ago and
one month ago.

Participants: The sample was composed of adult individuals
with a diagnosis of Graves’ disease, in thyrotoxicosis
(compensated or in hyperthyroidism), both genders,
attending a free university healthcare service of
ophthalmology in Sao Paulo, Brazil. Patients included in the
study read the consent form, agreed to participate and
signed it. They were divided into two groups according to
the presence or absence of exophthalmos.

Patients’ data of clinical history were collected in the
patients’ file to consider who were in clinical activity of the
Graves’ disease, and if they have presence or absence of
exophthalmos. Who met criteria of thyrotoxicosis
(compensated or in hyperthyroidism) with or without
exophthalmos, and signed the consent form was included in
the study, when the instruments started to be administered.

The study was performed between December/2004 to
December/2006.

Results

The sample consisted of a total of 82 patients diagnosed with
Graves’ disease, 63 of which were women (76.83%) and 19
were men (23.17%); with a minimum age of 18 and
maximum of 66 years. All patients were from the lower and
lower-middle economic classes, attending a free university
healthcare service in Sao Paulo, Brazil. Of the 82
participants, Group 1 (G1) consisted of 55 (67.07%)
individually with exophthalmos; 41 of which were women
(74.55%), with a mean age of 40, and 14 of which were men
(25.45%), with a mean age of 30.5 years. Group 2 (G2)
consisted of 27 (32.93%) individuals without exophthalmos;
22 of which were women (81.48%), with a mean age of 45.9
years and 5 of which were men (18.52%), with a mean age of
38.6 years.

Since there was no significant difference between frequency
of stress in men and women in both groups, the genders
were grouped for comparison as shown in Table 1. It can be

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seen from the statistical analyses of $X^2_{\text{calc}}=0.251$ that exophthalmos in Graves’ disease was not significantly associated with the presence of stress in the studied patients ($p=0.308$).

**Table 1.** Stress frequency in Graves’ Disease groups with (G1) and without (G2) exophthalmos.

<table>
<thead>
<tr>
<th>Group</th>
<th>G1 %</th>
<th>G2 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence</td>
<td>78.18</td>
<td>70.37</td>
</tr>
<tr>
<td>Absence</td>
<td>21.82</td>
<td>29.63</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

The possibility was also studied of a significant association existing between the frequency of stress in men and women in each group, considering the different age ranges, as shown in Table 2. However it was noted, from the Fisher’s Exact Test, that there was no significant association between the frequency of stress before and after the age of 44 for men ($p=0.442$) and women ($p=0.25$) in both groups.

**Table 2.** Stress Frequency in Graves’ Disease groups with (G1) and without (G2) exophthalmos by gender and age.

<table>
<thead>
<tr>
<th>AGE</th>
<th>G1</th>
<th>G2</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤44</td>
<td>70</td>
<td>60.61</td>
</tr>
<tr>
<td>&gt;44</td>
<td>30</td>
<td>39.39</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Since there was no significant association with frequency of depression in men and women in both groups, the genders were grouped for comparison as shown in Table 3. It can be seen from the statistical analyses of $X^2_{\text{calc}}=0.781$ that exophthalmos in Graves’ disease is not significantly associated with the presence of depression in the studied population ($p=0.188$).

**Table 3.** Depression Frequency in Graves’ Disease groups with (G1) and without (G2) exophthalmos.

<table>
<thead>
<tr>
<th>Group</th>
<th>G1 %</th>
<th>G2 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence</td>
<td>65.45</td>
<td>77.78</td>
</tr>
<tr>
<td>Absence</td>
<td>34.55</td>
<td>22.22</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

The possibility was also studied of a significant association existing between the frequency of depression in men and women in both groups, considering different age ranges, as shown in Table 4. It was seen from the Fisher’s Exact Test that there was no significant association between the presence of depression before and after the age of 44 for men ($p=0.335$) and women ($p=0.256$) in both groups.

**Table 4.** Depression Frequency in Graves’ Disease groups with (G1) and without (G2) exophthalmos by gender and age.

<table>
<thead>
<tr>
<th>AGE</th>
<th>G1</th>
<th>G2</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤44</td>
<td>80</td>
<td>65.38</td>
</tr>
<tr>
<td>&gt;44</td>
<td>20</td>
<td>34.62</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Next, a study was performed, by gender, on the concomitance of stress and depression in Graves’ disease patients with exophthalmos, since age was not a determining aspect of aggregate symptoms. It was seen from the McNemar test that there was a significant difference between the co-existence of stress and depression with exophthalmos ($p=0.033^*$) in women, while in men this co-existence of symptoms was not established ($p=0.688$) as shown in Table 5. The sample of men is too small to determine statistical significance.

Table 5. Percentage of Men and Women with concomitant stress and depression, with and without exophthalmos

<table>
<thead>
<tr>
<th></th>
<th>G1 Presence</th>
<th>G2 Presence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>Depression Only</td>
<td>Stress Only</td>
</tr>
<tr>
<td>Presence</td>
<td>4.88 (n=2)</td>
<td>21.95 (n=9)</td>
</tr>
<tr>
<td>Absence</td>
<td>0 (n=2)</td>
<td>0 (n=6)</td>
</tr>
<tr>
<td>Men</td>
<td>Presence</td>
<td>Stress Only</td>
</tr>
<tr>
<td>Presence</td>
<td>14.29 (n=2)</td>
<td>14.29 (n=2)</td>
</tr>
<tr>
<td>Absence</td>
<td>0 (n=2)</td>
<td>0 (n=2)</td>
</tr>
</tbody>
</table>

Women with exophthalmos add up to 100%: 4.88+21.95+58.54+14.63=100% (n=41)
Women without exophthalmos add up to 100%: 9.09+9.09+68.18+13.64=100% (n=22)
Men with exophthalmos add up to 100%: 14.29+14.29+57.13+14.29=100% (n=14)
Men without exophthalmos add up to 100%: 40.0+40.0+20.0=100% (n=5)

Discussion

The literature shows an extensive relationship between stress and Graves’ disease considering stress to be an influential aspect in the onset of the disease or in exacerbating its clinical course (Chiovato & Pinchera, 1996; Mizokami et al., 2004); since it produces changes in the neuroendocrine system and could modify the immune system activity that enables the expression of risk agents for auto-immunity. Therefore any other disease could be a potential risk to its presentation (Ader et al., 1995; Khansari et al., 1990), which depends on the genetic predisposition of each individual.

Although studies have shown patients with Graves’ disease to experience more stressful situations during their lives when compared to “normal” individuals (Chiovato & Pinchera, 1996; Mizokami et al., 2004), the findings of the present study showed that the frequency of stress on the studied sample is in line with the Lipp Inventory of Stress Symptoms for Adults results for the general Brazilian population (Lipp, 2000). This demonstrates that individuals with Graves’ disease, with or without exophthalmos, present the same behavior, as far as stress is concerned, as the general Brazilian population, with regard to age and gender. Differences between data in the literature and in this study may be due to the influence of the culture of the respective countries.

Despite the fact that no statistically significant association was noted between stress in the female population studied and age, women under the age of 44 with exophthalmos and women older than 44 without exophthalmos tend to exhibit a higher frequency of stress, as seen in Table 2. This shows that exophthalmos might not be acting as a cumulative sign of age-related stress but rather other factors might be contributing to this tendency, such as the hormonal factor in older women (APA, 2000; Soares et al., 2001), or aesthetic factors and their social consequences in younger women (Kenney, 2000). Similarly, men under the age of 44, with or without exophthalmos, also tended to have a higher frequency of stress, probably because of great social demands, rather than any aesthetic aspect.

In fact, the literature demonstrates an association between depression and thyroid disease (Dunlap & Moersch, 1935; Katshol et al., 1986) due to hormonal changes instigated by the disease that can directly influence mood. These changes could be acting directly on mood but there are more reported cases of mood swings than specific studies about depression in Graves’ disease (Irwin et al., 1997).

While no significant association was observed between frequency of depression and age for men and women with and without exophthalmos (as shown in Table 4), there was an inversion of the results concerning the presence of depression for each group with regard to age, which shows that exophthalmos might also not be acting as a cumulative sign of age-related depression.

Even though the sample of men was too small to obtain significance, a high frequency of depressed men was observed in both groups under the age of 44, which is in line with BDI data in terms of its validity to the Brazilian population (Cunha, 2001). On the other hand, women did not present any age-related differences in the validation of any of the studied BDI samples (psychiatric, medical and non-clinical). Therefore, men and women with Graves’ disease behave consistently in respect of age and the presence of depression.
However, an inversion can be seen with the frequency of depression in women with and without exophthalmos according to the age range under consideration. The high frequency of depression in younger women could be an emotional reaction to the aesthetic factor that accompanies exophthalmos and could play a role as a symptom aggregator in the first group (G1), while in older women without exophthalmos it could be due to climacteric and hormonal implications (Cury, 2003).

In any case, there are innumerable aspects that may contribute to the onset of depression and even so be independent of age, such as personality traits, chronic stress, unhappy childhood experiences, genetic influences, amongst others (Tanganelli, 2004; Soares et al., 2001; Kenney, 2000).

As a result, women with Graves’ disease and exophthalmos presented concomitance of symptoms, it being the exophthalmos and not Graves’ disease which is associated with the symptoms of stress and depression.

Given the high frequency of stress and depression noted in this study, it is important to undertake therapeutic intervention with the aim of finding the best way to deal with stress and treat depression during the clinical course and progression of Graves’ disease. New prevention programs are also a good option for reducing the risk of both symptoms, when available at the same time as the medical treatment.

Conclusion

Age was not a critical factor for the presence of stress or depression in the sample studied. Its incidence in the Graves’ disease population is approximately the same found in the Brazilian population, in general, for both genders, and therefore cannot be considered an aggregate symptom of the disease. The present study showed that exophthalmos is not associated with the presence of either stress or depression alone in men and women with Graves’ disease, but an association was found when the two diagnoses coexisted in the female sample. This correlation was not significant in men indicating a gender effect for the association of exophthalmos and stress plus depression combined. Furthermore, findings indicated that the significant association found was specifically between the compound of stress plus depression and exophthalmos but not between stress plus depression and Graves’ disease per se. Results lead to the conclusion that the critical factor for the appearance of the two conditions combined is the exophthalmos and not the Graves’ disease in general.

Recommendations for Further Studies

As a methodological limitation, the study used a small sample. Further studies should utilize larger samples to investigate if actually there are differences between genders in Graves’ disease. Future studies should also expand the age range to further assess possible differences in this variable. Considering that a concomitance of depression and stress was found in female patients with exophthalmos, it is suggested to evaluate the concomitance of stress and depression in patients that are indicted for surgery for orbital decompression since the orbital decompression is mainly indicated to improve the aesthetic aspect of the exophthalmos. The evaluation done before and after the surgery could elucidate if the depression/stress condition is the result of the aesthetical aspects of the condition.

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References


Address reprint request to Nara Lucia Poli Botelho:

R. Borges Lagoa, 1080 cj 906
Zip code 04038-002
São Paulo - Brazil.
e-mail: narapolibotelho@gmail.com