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A Survey Study of Neuropsychiatric Complaints in Patients with Graves' Disease

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One hundred thirty-seven patients with treated Graves' disease completed a questionnaire pertaining to neuropsychiatric complaints. Psychiatric symptoms, especially anxiety and irritability, were common prior to treatment of hyperthyroidism. These complaints appeared to result in delays in seeking treatment as well as delays in receiving appropriate diagnosis. Subjects reported significantly worse memory, attention, Planning and productivity while hyperthyroid than prior to becoming hyperthyroid, and, although somewhat improved once euthyroid, they reported residual cognitive deficits. These results suggest that neuropsychiatric impairments are highly prevalent in Graves' disease, may lead to initial misdiagnosis or delays in diagnosis of the endocrine disorder, and may continue even once patients are believed to be euthyroid.

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Disorders of the hypothalamic-pituitary-thyroid axis are often associated with neuropsychiatric impairments.¹ The presenting symptoms of Graves' disease, the most common cause of hyperthyroidism, are frequently psychiatric in nature, leading to possible difficulties in the differential diagnosis of hyperthyroidism and anxiety disorder.² Although many of the somatic symptoms of anxiety (such as tachycardia and tremor) may be caused by increased peripheral sympathetic tone secondary to thyrotoxicosis, several studies have suggested that additional psychiatric and cognitive impairments are also seen in hyperthyroid patients.³⁻¹⁰ These findings suggest a possible central effect, either due to alterations of brain thyroid hormone homeostasis or, perhaps, to autoimmune involvement in the brain.

The prevalence of neuropsychiatric impairments in Graves' disease is unknown because previous studies, which have had small sample sizes, have not addressed the issue of prevalence.

Furthermore, although clinical endocrinologists acknowledge that psychiatric and cognitive complaints are common in patients with Graves' disease, there have been no studies addressing the possible impact of these complaints on initial diagnosis and treatment. Finally, it is unclear whether the neuropsychiatric difficulties in Graves' disease follow a course parallel to the resolution of thyrotoxicosis⁵⁻¹¹ or remain after euthyroidism has been achieved.⁹⁻¹²

In this report, we present the results of a survey of the patient membership of the National Graves' Disease Foundation. The questionnaire addressed issues pertaining to the initial diagnosis and treatment of Graves' disease, the nature and extent of the psychiatric, somatic, and cognitive complaints of respondents when they were hyperthyroid, and assessment of residual complaints. This represents the first large-scale survey study of neuropsychiatric functioning in patients with Graves' disease.

Methods

An anonymous paper-and-pencil questionnaire was sent to all 240 patient members of the National Graves' Disease Foundation in March 1992. A cover letter describing the confidentiality and anonymity of the material was included, as was a postage-paid envelope to be used for returning the completed questionnaire. The questionnaire consisted of 24 items designed to assess pertinent demographic, diagnostic, and

well as the neurocognitive and emotional functioning of the respondents. Development of items was guided by advice from the National Graves' Disease Foundation and the findings of previous empirical studies of neuropsychiatric functioning in Graves' disease.²⁻⁵ One section focused on the length of time it took patients to seek treatment after the symptoms initially appeared and to be diagnosed after seeking help. To gain information on changes in psychiatric symptoms that could be related to Graves' thyrotoxicosis, a number of questions were asked regarding psychiatric referrals, diagnoses, and medications before and after the onset of Graves' disease. An extensive self-report section of symptoms experienced while hyperthyroid and after receiving treatment was designed to track common symptoms in an acute

hyperthyroid state as well as residual symptoms after euthyroidism was achieved. Visual analogue scales 100 mm in length with "good" and "poor" poles were created to measure subjective reports of neuropsychological functioning (memory, attention, planning, and productivity) before, during, and after the onset of Graves' symptoms.

Results

Of the 240 questionnaires distributed, 170 (70.8%) were

cluded because of one or more of the following: incomplete material, the presence of coexisting debilitating illnesses (such as muscular dystrophy or multiple sclerosis), disease onset that occurred either before age 21 or after age 65, or lack of a specific diagnosis of Graves' hyperthyroidism. There were then 137 eligible completed questionnaires. Of these, 127 (92.7%) were completed by women, and 10 (7.3%) were completed by men, with an age range of 21 to 78 years (mean SD = 48.1 11.5). The gender and age distributions in this sample are similar to those seen in Graves' disease in the general population.^{13,14} Table 1 presents pertinent demographic information of the sample.

Results of the questionnaire indicate that only 15% of

subjects sought treatment for Graves' disease symptoms within 1 month of initially experiencing the symptoms. In contrast, approximately 35% of respondents reported taking 6 months or more from the onset of Graves' symptoms to the time they sought treatment (Table 2). Approximately 35% of respondents reported that more than 3 months passed between the time they first sought treatment and the time

TABLE 1. Demographic characteristics

Characteristic	n	%
Gender		
Female	127	92.7
Male	10	7.3
Marital status		
Single	24	17.8
Married	76	56.3
Divorced	81	3.3
Separated	2	1.5
Never married	3	2.2
Living w/ other	12	8.9
Employment status		
Full-time	71	51.8
Part-time	21	15.3
Student	3	2.2
Homemaker	23	16.8
Disabled	14	10.2
Unemployed or looking	5	3.6
Income level		
< \$25,000	27	19.9
\$25,000-\$50,000	54	39.7
\$50,000-\$75,000	26	19.1
\$75,000-\$100,000	12	8.8
\$100,000-\$250,000	13	9.6
> \$250,000	4	2.9
Education level		
No high school diploma	2	1.5
High school diploma or GED	43	31.6
College/Technical	48	35.3
Master's	21	15.4
Doctorate	8	5.9
Other	14	10.3

they received an accurate diagnosis of Graves' disease (Table 3).

A variety of psychiatric symptoms were endorsed as being present while respondents were hyperthyroid. As shown in Table 4, the most common of these symptoms included irritability (78.1%), anxious mood (72.3%), anger (55.9%), and crying (55.1%). In addition, other signs and symptoms that are easily attributable to hyperthyroidism but are also cardinal features of psychiatric illness were frequently endorsed, such

as insomnia (66.4%), fatigue (65.7%), weight loss (62.8%), sensation of shakiness (65.4%), and shortness of breath (59.6%). Furthermore, only 7.7% of respondents reported ever being prescribed psychotropic medications prior to the 2 years before the onset of symptoms for Graves' disease, but 33.1% reported being prescribed psychotropic medications after being diagnosed with Graves' disease.

For all areas of functioning assessed on the self-report visual analogue scales, subjects reported significantly worse func-

tioning while hyperthyroid compared with the 2 years prior to the onset of hyperthyroid symptoms. Respondents reported that their current functioning, although better than during the hyperthyroid period, was significantly worse than during the premorbid time period (Table 5).

At the end of the questionnaire, there was a small space for any additional written comments the respondents wished to make. Surprisingly, 84% of the respondents used this space. In an attempt to quantify these written comments, we defined four areas of content, including 1) cognitive functioning, 2) mood or emotional functioning, 3) somatic complaints, and 4) complaints about medical care. Of the subjects who provided written comments, 24% described problems in cognitive functioning, most commonly involving slowed mental functioning and memory difficulties; 37% described altered mood or personality, most commonly involving depression, mood swings, and feelings of anxiety, panic, and worry; 50% reported having some physical symptoms, most commonly those related to eye disease (such as exophthalmos); and 11% described problems they have faced with their medical care related to Graves' disease, with the most common involving anger at the delay in diagnosis and complaints that

TABLE 2. Duration of time between first experiencing symptoms and seeking treatment

Duration	n	%	% (Cumulative) ^a
Less than 1 month	20	14.9	100.0
1-3 months	36	26.9	85.1
3-6 months	31	23.1	58.2
6 months to 1 year	21	15.7	35.1
More than 1 year	26	19.4	19.4

Note: Total n = 134; data not provided by 3 subjects.

^aPercentage waiting this long or longer to seek treatment.

TABLE 3. Duration of time between first seeking treatment and receiving Graves' diagnosis

Duration	n	%	%(Cumulative) ^a
Less than 1 week	41	30.2	100.0
1 week to 1 month	31	22.8	69.9
1-3 months	17	12.5	47.1
3-6 months	20	14.7	34.6
More than 6 months	27	19.9	19.9

Note: Total n = 136; data not provided by 1 subject.

^aPercentage waiting this long or longer to receive diagnosis.

their physicians either did not believe them or did not understand their symptoms. In many cases, subjects included a detailed history such as the following:

Before I was diagnosed I felt as though I was losing my mind. I couldn't get along well with others and my marriage was affected. I would go to the family doctor and he would say, "Oh, this is normal for a working mother of 3." I lost all self-confidence and worried a lot. I thought I had cancer or some other life-threatening disease. When I found a doctor that I was able to talk to and she understood, it was a wonderful moment!

Discussion

This report represents the first large-scale survey of the neuropsychiatric symptoms associated with Graves' hyperthyroidism. Results indicate that psychiatric symptoms are very common in the early presentation of Graves' disease and involve many of the mood and somatic features found in primary psychiatric illness, including anxiety, irritability, insomnia, anorexia, fatigue, dysphoria, hopelessness, and anger. These symptoms are severe enough that approximately one-third of the respondents reported being prescribed psychotropic medica-

TABLE 4. Prevalence of symptoms while respondents were hyperthyroid

Symptom	n	%
Irritability	107	78.1
Visible shakiness (especially in hands)	106	77.4
Feeling hot most of the time	101	73.7
Anxiety	99	72.3
Inability to sleep	91	66.4
Increased fatigue/weakness	90	65.7
Sensation of shakiness inside (but not visible)	89	65.4
Loss of more than 5 pounds in 3 months	86	62.8
Trouble breathing/shortness of breath	81	59.6
Change in hair or skin texture (e.g., dryness)	78	57.4
Anger	76	55.9
Increased crying	75	55.1
Easily startled	72	52.9
Inability to perform some daily tasks	68	50.0
Hot or cold flashes	65	47.8
Tired all the time	65	47.4
Significant decrease in social activity	62	45.6
Feelings of being out of control	61	44.5
Hopelessness	58	42.6
Sadness	57	41.9
Loss of sense of humor	56	41.2
Decreased sexual desire	55	40.1
Slowed thinking ability	54	39.7
Loss of interest in things that formerly gave you pleasure	53	39.0
Chest pain	51	37.5
Not being able to "connect" with others	46	33.8
Changes in menstrual cycle/Impotence	46	33.8

Table 5. Means and standard deviations for memory, attention, planning, and productivity visual analogue scales

Scale	Pre-Hyperthyroid	Hyperthyroid	Currently	F ^a			
Memory	77.68	18.18	47.56	31.23	55.39	25.93	69.77
Attention	74.75	20.59	40.36	29.39	55.76	25.14	80.88
Planning	75.06	19.97	45.66	29.93	60.11	25.09	61.95
Productivity	76.31	19.14	41.99	31.53	55.79	25.72	73.55

Note: All scales had possible range of 0-100, with higher scores representing better perceived functioning.

^aMain effects tested with repeated-measures analyses of variance. All resulting Fs were significant, $P < 0.001$. Post hoc pairwise comparisons were performed by using Tukey's honestly significant difference test; all were significant, $P < 0.001$.

tions after their diagnosis of Graves' disease. With regard to cognitive functioning, respondents reported a significant decline in memory, attention, planning, and overall productivity from the time period 2 years prior to Graves' symptom onset

With regard to cognitive functioning, respondents reported a significant decline in memory, attention, planning, and overall productivity from the time period 2 years prior to Graves' symptom onset to the period when hyperthyroid.

to the period when hyperthyroid. It is noteworthy that although subjects reported their cognitive functioning was improved relative to the hyperthyroid period, they felt that their current functioning still was worse than it was prior to the onset of the disease.

A striking secondary finding of this study was that 84% of the respondents provided written comments describing their history of Graves' disease. These descriptions may shed some light on the findings that the majority of subjects waited more than 3 months before seeking medical help for their

Graves'-related symptoms and that for almost half of the respondents it took more than 1 month to receive an accurate diagnosis after first seeking help. Many of the initial symptoms of Graves' disease are not at all specific to the illness. In fact, as reported in previous studies^{2,14} and further supported by the results of this study, neuropsychiatric complaints can be the presenting symptoms of Graves' disease. Many patients who first experience these symptoms (such as irritability, anxiety, fatigue, or weight loss) may hesitate to seek medical help because they believe they are merely experiencing temporary anxiety or are embarrassed to seek help for such "Personal" problems. Unfortunately, it appears that some health care providers (and mental health care providers, who may first see these patients) too quickly dismiss the symptoms as representing primary psychiatric disorders rather than manifestations of the underlying endocrinopathy.

The neuropsychiatric impairments associated with Graves' disease not only have dramatic effects on the patient, but also frequently affect the patient's support system. The psychiatric, cognitive, and personality changes that occur with this illness can produce significant marital stress and conflict, as described in a recent open letter

to the spouses of Graves' patients that appeared in the National Graves' Disease Foundation's newsletter:

In a lot of ways my wife and I were fortunate. She was diagnosed with Graves' disease after approximately nine months; at least that is the closest she and I can pinpoint when she began to first experience the symptoms we now associate with Graves'. During that time, however, while I always knew my wife loved me, frequently who I was married to was not my wife. one aspect was the mood swings, the unexpected outbursts of anger and accusation, the unexplainable crying. This took the most work for me to deal with emotionally.¹⁵

The survey format of this study allowed for a relatively large sample to be assessed.

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Moreover, the anonymity of the questionnaire probably contrib-

uted to the very high return rate and the many open-ended written responses. However, there are several limitations to this design that may hamper the generalizability and overall interpretation of the findings. By definition, this format relies on retrospective recall and subjective report of psychiatric and cognitive symptoms; both of these modes are potentially highly unreliable and may result in artificial inflation of symptom reports. Retrospective recall of the timing of symptom onset is also of questionable reliability, and there was no objective verification of the length of time between first seeking medical help and accurate diagnosis. The anonymity of the questionnaire also precludes verification of Graves' diagnosis or the obtaining of thyroid hormone levels. There may also be sample bias due to the use of the membership of the National Graves' Disease Foundation; that is, those individuals who seek out membership in such an organization may have very different neuropsychiatric profiles (both

before and after onset of Graves' disease) from other Graves' patients not belonging to this kind of organization. Furthermore, although there was an extremely high response rate, it is still possible that these data are not truly representative even of the entire membership of the Foundation. To address these limitations, a large-scale, longitudinal, prospective, objective neuropsychiatric study of newly diagnosed Graves' patients would be necessary.

Even if the results of the present study are conservatively interpreted, it appears that neuropsychiatric symptoms are common in Graves' disease, may continue even after peripheral euthyroidism has been achieved, may lead to difficulties in differential diagnosis, and represent a significant area of morbidity and stress associated with this autoimmune-related endocrine disorder. Involvement of mental health care providers who are familiar with neuropsychiatric differential diagnostic issues should prove

helpful in the management of patients with Graves' disease, both at initial presentation and later in the course of illness.

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