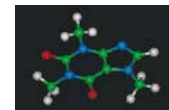# Refractory Nonmotor Symptoms in Male Patients With Parkinson Disease Due to Testosterone Deficiency

A Common Unrecognized Comorbidity

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Background: Many patients with Parkinson disease (PD) suffer from nonmotor symptoms including depression, anxiety, sexual dysfunction, decreased energy level, and an overall decline in quality of life. Comorbid depression, hypothyroidism, and sleep disorders may account for some, but not all, of these problems. Testosterone deficiency affects 20% to 25% of males over the age of 60 years in the general population and may cause signs and symptoms of the nonmotor symptoms seen in PD. We observed numerous patients with PD whose nonmotor symptoms were refractory to treatment.

Objective: To determine whether treatment of comorbid testosterone deficiency in male patients with PD can lead to improvements in refractory nonmotor symptoms.

Methods: Case studies were reviewed of the first 5 male patients who had PD with symptoms of testosterone deficiency who were treated in our clinic. All patients had low serum testosterone levels. Screening for testosterone deficiency symptoms using the St Louis Testosterone Deficiency Questionnaire was performed for 4 of the 5 patients. Additionally, to assess the prevalence of PD, total testosterone levels in 68 patients in our PD registry were sent for evaluation.

Results: Following testosterone replacement therapy, all 5 patients experienced significant improvements in their refractory nonmotor symptoms. Of 68 male patients with PD enrolled in our PD registry, 24 (35%) had plasma evidence of testosterone deficiency. We also noted that the risk of testosterone deficiency per decade was found to increase 2.8-fold per decade ($P<.001$), paralleling that which is found in the general elderly male population.

Conclusions: The findings from this study reveal the heretofore unrecognized high prevalence of testosterone deficiency in elderly male patients with PD similar to that found in the general population. These symptoms, which may be refractory to antidepressants, anxiolytics, and antiparkinsonian medications, may respond to treatment with testosterone. More rigorous controlled studies will need to be undertaken to examine the treatment of this common comorbidity in male patients with PD.

Arch Neurol. 2002;59:807-811

P ARKINSON DISEASE (PD) is a progressive neurodegenerative disorder characterized by both motor and nonmotor signs and symptoms. Although attention has focused largely on the motor aspects such as bradykinesia, rigidity, tremor, and gait difficulties, of equal, and often even greater importance are the nonmotor symptoms that affect quality of life such as depression, anxiety, sexual dysfunction, and cognitive impairment. In some cases comorbid conditions such as depression, hypothyroidism, and sleep disorders may account for some of the nonmotor symptoms. Recognition of these comorbid conditions is important because, when untreated, they may contribute significantly to the clinical burden. In male patients with PD, we have identified an additional comorbidity, testosterone deficiency. Testosterone deficiency is found in 20% to 25% of the adult males older than age 60 years (depending on age) and is a well-documented cause of depression, fatigue, decreased libido, and decreased work performance.[1-4] These deficiency symptoms respond favorably to testosterone replacement therapy (TRT).[3,5-7]

We report our experience with TRT in 5 males with combined PD and symptoms of testosterone deficiency. Such patients were poorly responsive to antiparkinsonian and antidepressant medications. We observed significant clinical improvement in specific nonmotor symptoms with the administration of TRT. We also report the high prevalence of low testosterone levels in patients enrolled in our PD registry.

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PATIENTS AND METHODS

We present the results of a retrospective analysis of the first 5 patients who were seen with combined PD and symptoms of testosterone deficiency. Patients seen after our initial index patient were screened for testosterone deficiency using the validated St Louis Testosterone Deficiency Questionnaire (SLTDQ) (**Table 1**).[8] Patients who met SLTDQ criteria were then screened for total and free testosterone levels (**Table 2**). Patients with levels of free testosterone less than 70 pg/mL with no potential medical contraindications to TRT including sleep apnea, polycythemia, prostate cancer, urinary outlet obstruction, or congestive heart failure were treated with a testosterone gel (AndroGel; Unimed Pharmaceuticals Inc, Deerfield, Ill), 5 g/d, applied locally to the skin. Prostate-specific antigen studies and a digital rectal examination were performed to exclude the presence of prostate cancer. Unified Parkinson's Disease Rating Scale motor scores were also recorded.

To better assess the prevalence of low testosterone levels in PD, we assessed total testosterone levels in male patients with PD enrolled in our PD registry with a confirmed diagnosis of idiopathic PD. A multiple linear regression model was used to analyze the potential increase in risk of testosterone deficiency per decade.

There is, as yet, no universally accepted testosterone value (total testosterone or free testosterone) that defines an older man as being testosterone deficient.[1] Many investigators in the field have used testosterone levels at or below the lower limit of normal for young adult men as their working definition of testosterone deficiency, or older male "hypogonadism."[1] Using the large Baltimore Longitudinal Study data set, Harman et al[2] have defined older men as being hypogonadal if their total testosterone plasma level was below 325 ng/dL (11.3 nmol/L), or their free testosterone index was less than 0.153.[2] We extrapolated, based on the more sensitive test for testosterone deficiency, free testosterone, a level of less than 70 pg/mL to define testosterone deficiency.

RESULTS

Five patients were treated with daily applications of testosterone gel who had free testosterone levels of 56 pg/mL or less (averages: free testosterone level, 37.6 pg/mL; total testosterone level, 243.6 ng/dL [8.4 nmol/L]). Following TRT all patients experienced significant improvement in refractory nonmotor symptoms of PD, especially fatigue, depression, anxiety, and sexual dysfunction. Parkinsonian features seemed to improve in several men, but we were unsure whether these improved secondarily as a result of the improvement in mood and energy or if TRT had a direct effect. Data from the first 5 cases that we have encountered and treated with TRT are summarized in Tables 1 and 2 with individual case descriptions presented below.

CASE 1

An 87-year-old man had a 7-year history of PD with tremor, rigidity, bradykinesia, and unsteady gait. After experiencing an excellent response to levodopa replacement therapy for many years, over the span of 1 year he experienced a rather marked decline with depressed mood, fatigue, decreased energy level, and an overall withdrawal from life and decreased well-being. He was diagnosed as having depression and had therapeutic trials of buproprion, sertraline, and paroxetine, and multiple adjustments of his antiparkinsonian medications with little effect on his symptoms. His plasma free testosterone level was 42 pg/mL and his total testosterone level was 305 ng/dL (10.6 nmol/L).

A 1-month follow-up visit after receiving TRT revealed marked improvements in mood, energy, libido, and well-being. His PD symptoms were improved with regard to gait and balance, but it was unclear whether this improvement was due to TRT or to an adjustment of his dosage of fludrocortisone acetate (Florinef; Apothecon, Bristol-Myers Squibb Co, Princeton, NJ) that was being used for symptomatic orthostatic hypotension.

CASE 2

An 87-year-old man with a 12-year history of tremor-predominant PD reported 5 years of progressively worsening depression, anxiety, and other nonmotor symptoms. His PD symptoms were optimally treated with antiparkinsonian medications. He was treated with therapeutic doses of sertraline with a partial improvement in his mood and anxiety symptoms. His SLTDQ score was positive for 7 of 10 symptoms (Table 1). His plasma free testosterone level was 25 pg/mL; his total testosterone level was 166 ng/dL (5.8 nmol/L).

After 1 month of receiving TRT, his SLTDQ score reflected improvement in libido, and during the patient interview he reported significant improvements in mood, anxiety, and libido. During the month of treatment his quality of life improved on the Parkinson Disease Quality of Life Questionnaire especially in the categories of activities of daily living, mobility, and emotional well-being. He felt his parkinsonism was improved although there was no change in his Unified Parkinson's Disease Rating Scale motor scores before and after TRT.

CASE 3

A 59-year-old man with a 7-year history of tremor-predominant PD developed significant depression that was not relieved by therapeutic trials of citalopram and venlafaxine. His PD symptoms were optimally treated with antiparkinsonian medications. His SLTDQ score was positive for 6 of 10 symptoms (Table 1). His free testosterone level was 55.5 pg/mL; his total testosterone level was 353 ng/dL (12.2 nmol/L).

On a follow-up visit 4 months after beginning TRT, he reported that within weeks of beginning treatment there was a sustained and marked improvement in his mood and strength. Both libido and erectile dysfunction had improved and he no longer felt depressed. He

Table 1. Pretreatment (Pre) and Posttreatment (Post) Patient Responses to the St Louis Testosterone Deficiency Questionnaire*

St Louis Testosterone Deficiency Questionnaire†	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1. Do you have a decrease in libido?	NA	NA	•		•		•	•	•	
2. Do you have a lack of energy?	NA	NA	•	•			•		•	•
3. Do you have a decrease in strength or endurance?	NA	NA	•	•	•	•	•		•	•
4. Have you lost height?	NA	NA	•	•			•		•	•
5. Have you noticed a decreased enjoyment of life?	NA	NA			•		•		•	•
6. Are you sad or grumpy?	NA	NA				•	•			
7. Are your erections less strong?	NA	NA	•	•	•		•	•	•	
8. Are you falling asleep after dinner?	NA	NA	•	•			•	•		
9. Have you noted a recent deterioration in your ability to play sports?	NA	NA	•	•	•		•	•	•	
10. Has there been a recent deterioration in your work performance?	NA	NA			•		•		•	•
Pre and Post TRT Scores	NA	NA	7	6	6	2	10	4	8	5

*NA indicates information not available; •, positive response to St Louis Testosterone Deficiency Questionnaire; and TRT, testosterone replacement therapy.
†A presence of 1 or more of the following criteria indicates a positive St Louis Testosterone Deficiency Questionnaire: a positive response to question 1; a positive response to question 7; or a positive response to any 3 of the other questions.

Table 2. Patients Treated for Parkinson Disease (PD) and Testosterone Deficiency

Patient Age, y	Duration of PD, y	Free Testosterone Level, pg/mL	SLTDQ Score*		Motor Symptom†	Nonmotor Symptom†			No. of Antidepressant Trials
			At Baseline	At Baseline, 1 mo		Depression	Libido	Anxiety	
87	7	42.2	NA	NA	+	+++	++	NA	>2
87	12	25.0	7/10	6/10	+	+++	++	+++	>2
59	7	55.5	6/10	2/10	+	+++	+	NA	2
59	20	31.9	10/10	4/10	+	+++	+	+++	2
73	12	33.2	8/10	5/10	+	+++	+	NA	2

*SLTDQ indicates St Louis Testosterone Deficiency Questionnaire; numerator, number of criteria met; denominator, total possible score; and NA, not available.
†Motor and nonmotor symptom improvement at 1 month: + indicates mild improvement; ++, moderate improvement; +++, complete or nearly complete improvement.

reported increased involvement and satisfaction with his daily activities. His SLTDQ score improved from 6 positive symptoms to 2 positive symptoms (Table 1). There was a slight improvement in his Unified Parkinson's Disease Rating Scale motor score.

CASE 4

A 59-year-old man who had idiopathic PD for 20 years noted worsening and intractable depression over several months. He had undergone a right-sided pallidotomy 7 years earlier for treatment of dyskinesias. His symptoms included tremor, bradykinesia, on-off motor fluctuations, dyskinesias, fatigue, and depression. His parkinsonian symptoms were optimally treated with antiparkinsonian medications, and he had been treated previously with therapeutic doses of citalopram and venlafaxine without improvement in depression and nonmotor symptoms. His SLTDQ score was positive for all 10 symptoms of testosterone deficiency (Table 1). His plasma free testosterone level was 31.9 pg/mL; his total testosterone level was 162 ng/dL (5.6 nmol/L).

At a 1-month follow-up visit after starting TRT, he reported a marked improvement in depression, anxiety, and overall strength. He was again able to mow his lawn and perform yard work unassisted. His SLTDQ score improved after TRT from 10 to 4 positive symptoms (Table 1). He reported improvement in PD symptoms particularly in regard to his overall mobility and gait, but also noted some worsening of his dyskinesias.

CASE 5

A 73-year-old man with idiopathic PD for 12 years with tremor, rigidity, bradykinesia, and gait difficulties presented with reports of increasing fatigue and depression. He had undergone a left-sided pallidotomy 5 years prior to presentation for treatment of dyskinesias. He was previously treated with therapeutic doses of sustained-release buproprion and venlafaxine without a change in his depressive symptoms. His SLTDQ score was positive for 8 of 10 symptoms (Table 1). His plasma free testosterone level was 33.2 pg/mL; his total testosterone level was 232 ng/dL (8.0 nmol/L).
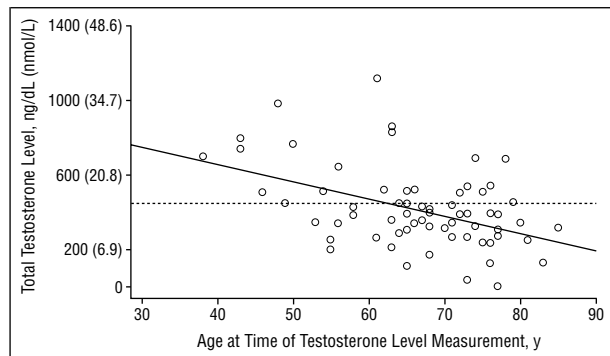
Risk of testosterone deficiency with age in 64 male patients with Parkinson disease (PD) entered in the Parkinson Disease–Alzheimer Disease Registry, Emory University, Atlanta, Ga.

At a 1-month follow-up visit after receiving TRT, he reported marked improvement in his depression symptoms including mood, energy, and anhedonia. His SLTDQ score improved to only 5 of 10 positive symptoms with his most marked improvements in libido and erectile dysfunction (Table 1). His PD symptoms also improved, however, it was unclear whether adjustments in his levodopa and dopamine agonist dosages along with his improvement in mood were responsible for the motor improvement he exhibited.

RESULTS OF PREVALENCE OF TESTOSTERONE DEFICIENCY IN A PD REGISTRY

Data derived from a PD registry showed an age-related decline in testosterone levels in 68 male patients with PD. Twenty-four male patients with PD (35%) in this registry had low testosterone levels (<325 ng/dL [<11.3 nmol/L]). A multiple linear regression model revealed a 2.8-fold increase per decade in risk of testosterone deficiency in male patients with PD (**Figure**). The results indicated a significant relationship between age and testosterone deficiency in male patients with PD ($P<.001$), as is found in the general male population older than 60 years.[1,2]

COMMENT

The findings from this study points to the heretofore unrecognized high prevalence of testosterone deficiency in male patients with PD. The prevalence of low testosterone levels in a PD registry (24 patients [35%]) is considerably higher than that in the general male population over the age of 60 years with increasing prevalence for each decade.[1,2] The high prevalence of low testosterone levels found in a PD registry may be higher than the general population with PD because of a referral bias, ie, refractory patients were referred for a second opinion or for surgery. Further studies will be needed to determine the true prevalence of low testosterone levels in patients with PD.

Patients who have PD with low testosterone levels typically exhibit nonmotor symptoms suggestive of depression and anxiety, ie, decreased libido, decreased energy, decreased endurance, and anhedonia. Most striking in this patient group was the refractoriness of the

symptoms to optimal parkinsonian, antidepressant, and anxiolytic treatments. In this respect they were similar to patients with unrecognized hypothyroidism who are also poorly responsive to these treatments.[9-11]

Numerous studies in the geriatric population have revealed that testosterone deficiency symptoms such as lack of energy, fatigability, irritability, anxiety, and depression will respond to TRT.[3-5,12-16] Patients with depression refractory to antidepressant medication in the setting of testosterone deficiency have also been shown to respond to TRT. In the study by Seidmann and colleagues,[3,17] all of the men treated had significant improvement in their symptoms of depression. Additionally, symptoms of depression have been treated successfully with testosterone in men with human immunodeficiency virus–infected symptomatic hypogonadism.[18,19]

Since 1948 it has been known that treatment of men with low testosterone levels can improve deficiency symptoms.[20] Functional improvement in rehabilitation scores and grip strength improved in men receiving TRT and increased their rehabilitation potential.[21] Logistically, older men who have PD and testosterone deficiency should also benefit by TRT. Since patients with PD are prone to falling, improvements in strength and rehabilitation potential are important for their long-term management. Clinicians should consider screening elderly male patients with PD who have treatment refractory nonmotor symptoms of PD for the treatable and common comorbidity of testosterone deficiency, before attributing symptoms directly to PD.

Data from the PD registry (Figure) reported in this article should increase awareness of a common and treatable comorbidity in this population. This comorbidity should not be confused with nonmotor symptoms that are a direct result of PD. Testosterone levels decline with normal aging probably secondary to a decline in Leydig cell functioning. Although the rate of decline can vary greatly between individuals, both cross-sectional and longitudinal studies, in general, have confirmed this decline.[2,22,23] Long-term illness and certain medications are associated with lower testosterone levels.[24,25] A significant proportion of older men (perhaps 20%) will experience a decline in the level of testosterone to the extent that they will develop symptoms of testosterone deficiency.[1,5]

Although the men in our study experienced improvement in mobility, it was unclear whether this was a primary or secondary effect of TRT. To our knowledge, there have been no prior clinical studies of the effects of TRT on motor and nonmotor symptoms in PD. Since androgen receptors have been found to anatomically co-localize with dopamine neurons in the midbrain and hypothalamus,[26,27] TRT may conceivably have an effect on the motor symptoms in PD. More studies will be needed to evaluate the efficacy of TRT on motor symptoms of PD. Additionally, it has been suggested that androgens may play a neuroprotective role in some neurodegenerative diseases. Estrogen has been observed to promote in vitro neurite growth in the mesencephalon of tyrosine hydroxylase immunoreactive neurons,[28] and a recent study revealed that estrogen coadministered with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine was neu-

roprotective against the loss of substantia nigra cells in primates,[29] and in males, testosterone is the major source of estrogen.

It is unknown whether testosterone deficiency and PD represent independent entities, ie, comorbidities that overlap, and whose symptoms are simply additive or whether testosterone deficiency may influence age of onset, the rate of progression, overall clinical severity, and specific nonmotor and motor features of the disease. Although all patients showed improvement in their symptoms of testosterone deficiency, since there may be a large placebo effect in therapy with testostrone or estrogen, a blinded, placebo-controlled study is clearly necessary to demonstrate clinical efficacy. The finding, however, that the prevalence of PD in males outnumbers females by a significant extent[30] may be due in part to the effect of testosterone deficiency in males older than 60 years. Finally, it remains to be determined whether a low testosterone level could contribute to the clinical picture in other neurodegenerative diseases affecting older males such as Alzheimer disease, stroke, and neuromuscular disease. Such questions will necessarily remain for future epidemiological and clinical studies to address.

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