bent to the left. Without assistance she could not easily stand up, and her feet quickly froze when she attempted to walk forward. Shuffling hesitant steps were more marked on the left side and were particularly evident when turning, initiating gait, and walking backwards (fig 1A). They were not alleviated by visual aids such as stripes on the floor or by the use of an inverted walking cane. Her facial expression and speech were slightly affected and she manifested micrographia. On medication, her total and Part III motor scores on the Unified Parkinson's Disease Rating Scale were 38 and 19, respectively. Magnetic resonance imaging (MRI) revealed no obvious abnormalities except for the surgical lesions produced 20 years earlier in the bilateral thalamic nuclei (fig 1B, C). Because she had experienced occasional transient drug induced psychoses that disappeared when the dosages were reduced, we concluded that it was not possible to improve her symptoms by pharmacotherapy alone and decided to perform stereotaxy. Prior informed consent was obtained from the patient and her family.

STN stimulation using two ventral contacts (contacts 0 and 1) gave rise to a striking improvement of her axial symptoms. Contacts 0 and 1 were used as cathode (fig 1D) and the pulse generator as anode. After extensive trials, the optimal stimulation parameters were determined to be 130 Hz frequency, 60 μsecond pulse width, and 1.8 V and 2.6 V amplitude at the first and final session, respectively. Under stimulation, she was able to stand up with ease and without assistance, and could initiate gait fluently. Her shuffling hesitant steps almost disappeared even when turning and walking backwards (fig 1E). Compared to preoperative baselines, her total and Part III motor scores were reduced from 38 and 19 to 11 and 5, respectively. She continued to take the same medication at the same doses as before and the beneficial effects of STN stimulation were unchanged at 9 months post-treatment.

Medically intractable PD has been addressed with different types of surgery. Our patient initially underwent staged bilateral thalamotomy. Although this procedure produced long lasting benefits and her tremor, rigidity, and dyskinesias were improved, bilateral, even staged, thalamotomy carries significant risks and is no longer considered a viable treatment option.[2] Nonetheless, we recognised the long lasting effectiveness of bilateral thalamotomy; our patient was operated on 20 years earlier by Dr. Narabayashi.[1] However, because of the recent aggravation of her axial parkinsonian symptoms, for which thalamotomy is generally thought to be ineffective,[2] she was referred to our hospital for further treatment.

While STN DBS can markedly improve all levodopa responsive motor features of parkinsonism including axial symptoms,[6] STN DBS appears to exhibit greater anti-parkinsonian effects than GPi DBS. Therefore, we chose STN stimulation for our patient. We initially thought that bilateral surgery was necessary. However, we found that unilateral (right) STN DBS contralateral to the more severely affected side markedly alleviated her axial symptoms, and led to the almost complete disappearance of her shuffling, hesitant steps and falling. At present, we do not know whether she will eventually require additional contralateral (left) STN DBS.

In patients with PD, various combinations of different stereotactic interventions have produced varying results and there is currently no consensus regarding their efficacy [for examples, see references 7 and 8]. Based on the experience reported here, we suggest that PD patients with a prior successful thalamotomy may be good candidates for STN stimulation.

S Goto, K Yamada, Y Ushio

Department of Neurosurgery, Kumamoto University Medical School, Kumamoto 860-8556, Japan

Correspondence to: Dr S Goto, Department of Neurosurgery, Kumamoto University Medical School, Kumamoto 860-8556, Japan; sgoto@kaiju.medic.kumamoto-u.ac.jp

References

1 **Narabayashi H**. Surgical treatment in the levodopa era. In: Stern G, ed. *Parkinson's disease*. London: Chapman & Hall, 1990:597–646.
2 **Hallett M**, Litvan I, the Task Force on Surgery for Parkinson's Disease. Evaluation of surgery for Parkinson's disease: a report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. *Neurology* 1999;**53**:1910–21.
3 **Lang AE**. Surgery for levodopa-induced dyskinesias. *Ann Neurol* 2000;**47**(Suppl):S193–9.
4 **Limousin P**, Krack P, Pollak P, *et al*. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 1998;**339**:1105–11.
5 **Kumar R**, Lozano AM, Kim YJ, *et al*. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. *Neurology* 1998;**51**:850–5.
6 **Bejjani B-P**, Gervais D, Arnulf I, *et al*. Axial parkinsonian symptoms can be improved: the role of levodopa and bilateral subthalamic stimulation. *J Neurol Neurosurg Psychiatry* 2000;**68**:595–600.
7 **Houeto JL**, Bejjani PB, Damier P, *et al*. Failure of long-term pallidal stimulation corrected by subthalamic stimulation in PD. *Neurology* 2000;**55**:728–30.
8 **Moro E**, Esselink RAJ, van Blercom N, *et al*. Bilateral subthalamic nucleus stimulation in a parkinsonian patient with previous unilateral pallidotomy and thalamotomy. *Mov Disord* 2000;**15**:753–4.

Testosterone deficiency in a Parkinson's disease clinic: results of a survey

It has been shown recently that male patients with Parkinson's disease who have testosterone deficiency may have symptoms resembling non-motor parkinsonian symptoms.[1 2] Because of the similarity between the non-motor symptoms of Parkinson's disease and the symptoms of testosterone deficiency, clinicians may fail to recognise and treat testosterone deficiency in patients with Parkinson's disease.[1] The identification of testosterone deficiency may have a significant impact on the long term course of the disease, as symptoms mistakenly labelled as non-motor parkinsonian manifestations could be relieved more effectively by testosterone replacement than by other treatments.

In this study we examined the prevalence of testosterone deficiency and testosterone deficiency symptoms among a group of patients with Parkinson's disease presenting to our movement disorders clinic, to assess how common undiagnosed symptomatic testosterone deficiency was in this population. A mail-back survey was administered to all the patients seen in the clinic after a 12 month period where patients were seen, examined, and entered into a database. The surveys were returned by 91 of 137 male patients with Parkinson's disease (66%). The diagnosis of idiopathic Parkinson's disease was confirmed by a movement disorders specialist who applied the UK Brain Bank criteria[3] and currently recommended guidelines for the diagnosis of Parkinson's disease.[4] We included in the survey two validated scales—the St Louis testosterone deficiency questionnaire[5] and the Beck depression inventory.[6 7] Additionally, historical information was obtained including the number of antidepressants the patients were exposed to in a lifetime, number of current antidepressants, history of testosterone deficiency, history of prostate cancer, and history of hormone replacement therapy. Forty two male patients with Parkinson's disease who returned questionnaires had previously been identified as testosterone deficient by measurements of plasma testosterone concentrations.

The results of the survey are summarised in table 1. The average age of the male patients was 62 years. Nine per cent of the study population were on testosterone gel replacement therapy. Fifty of the 91 patients with Parkinson's disease were screened with free testosterone levels during the 12 month period of the study. Half of the Parkinson's disease patients (n = 25) who were screened for testosterone deficiency had a level of <70 pg/ml and were defined as having ''low'' testosterone. Ninety per cent of all male patients with Parkinson's disease had a positive St Louis testosterone deficiency questionnaire (positive answers to more than three questions).

Comment

The results of our survey indicate that testosterone deficiency is common in the elderly male population seen in a movement disorders clinic setting, and the prevalence is similar to that previously reported in the Baltimore longitudinal study of aging in the normal elderly population[8] and in Parkinson's disease.[1] As the non-motor symptoms of Parkinson's disease—including depression, anxiety, fatigue, decreased libido, sexual dysfunction, and a decreased enjoyment in life—directly overlap with those seen in male testosterone deficiency, separating testosterone deficiency from the non-motor symptoms of Parkinson's disease can be difficult. This separation is important because specific treatment for testosterone deficiency is available and because these symptoms may not respond satisfactorily to antidepressant therapy.

Previous observations of refractory non-motor symptoms of Parkinson's disease that responded to testosterone replacement suggested that patients were on or had been exposed to an increased number of antidepressants.[1] Seidman and Rabkin found that testosterone deficiency—as also seen in thyroid hormone deficiency—may blunt responsiveness to antidepressants,[9] prompting the investigators to examine whether patients with testosterone deficiency took more antidepressants than those without testosterone deficiency, as well as to examine whether deficiency scores correlated with the number of antidepressants. Our data did not suggest a difference in antidepressant use in the testosterone deficient Parkinson's disease

Table 1 Characteristics of 91 male patients with Parkinson's disease who returned the questionnaire

Characteristic		All (n = 91)	Free T <70 pg/ml (n = 19)	Free T >70 pg/ml (n = 23)
Age (years)				
Mean		64	71	61
SD		10	9	10
Range		40 to 89	55 to 89	44 to 83
HRT (% of patients)		10%	21%	4%
Free testosterone level (pg/ml)				
<70		19 (45%)	19 (100%)	0 (0%)
>70		23 (55%)	0 (0%)	23 (100%)
Mean		82.1	49.0	109.4
SD		41.6	13.6	36.7
Range		4.1 to 196.1	4.1 to 65.7	71.2 to 196.1
St Louis score				
⩾3		85 (93%)	18 (95%)	22 (96%)
<3		6 (7%)	1 (5%)	1 (4%)
Mean		5.9	6.6	5.8
SD		2.3	2.2	2.2
Range		0 to 10	2 to 10	2 to 10
BDI score				
Mean		9.2	10.5	9.3
SD		6.0	6.7	5.4
Range		0 to 31	2 to 22	0 to 19
Number of antidepressants				
Current:	0	51 (56%)	7 (37%)	13 (57%)
	1	37 (41%)	11 (58%)	10 (43%)
	>1	3 (3%)	1 (5%)	0 (0%)
Lifetime:	0	35 (38%)	4 (21%)	9 (39%)
	1	27 (30%)	10 (53%)	4 (17%)
	2	15 (16%)	1 (5%)	6 (26%)
	3	10 (11%)	3 (16%)	2 (9%)
	>3	4 (4%)	1 (5%)	2 (9%)

BDI, Beck depression inventory; HRT, hormone replacement therapy; T, testosterone.

population; however, a prospective study will need to be done to confirm this observation. Overall, however, depression scores were not high in this study, which may either reflect aggressive treatment of depression in our Parkinson group, or suggest that testosterone deficiency does not present as major depression. Additionally, the study did not specifically screen for patients who were refractory to antidepressant treatment, and for those who had previously received aggressive treatment for depression. We suspect that testosterone deficiency, like thyroid deficiency, does affect the efficacy of antidepressants, but better prospective studies will be needed to examine this question.

Testosterone deficiency is a common, treatable, and largely unrecognised form of comorbidity in Parkinson's disease, and as demonstrated by this study is common in a movement disorders clinic setting. It may go undiagnosed when the symptoms are attributed to the non-motor manifestations of Parkinson's disease. Additionally, a lack of a history of refractoriness to antidepressants, or lack of a positive depression screening questionnaire, should not dissuade practitioners from checking testosterone levels, as antidepressant responsive ''depressive symptoms'' seem to be common in testosterone deficiency.

Prospective epidemiological studies on this topic need to be undertaken, as this analysis of clinic patients suffered from both the bias of the researchers interested in testosterone deficiency, and the failure to get 100% return of the surveys. Additionally, a control group will need to be included in future analyses, and better screening devices with increased specificity for patients with Parkinson's disease and testosterone deficiency will need to be developed. The issue of which type of testosterone assay is best, and how much the testosterone level matters if a patient is symptomatic, will also need to be examined.

Every practitioner who sees patients with Parkinson's disease should be aware of this common treatable co-morbidity. The diagnosis of testosterone deficiency should be confirmed and prostate cancer excluded before initiating treatment.

Acknowledgements

We would like to thank the American Parkinson's Disease Association and the Department of Neurology and McKnight Brain Institute for their generous support and help with the research described in this report.

M S Okun, G P Crucian
Department of Neurology, McKnight Brain Institute, University of Florida, USA

L Fischer, B L Walter, C M Testa, J L Vitek, M R DeLong
Department of Neurology, Emory University

J Hanfelt
Department of Biostatistics, Emory University

X Huang
Department of Neurology, University of North Carolina, Chapel Hill

Correspondence to: Dr Michael S Okun, Movement Disorders Center, University of Florida, Brain Institute, PO Box 100236, Gainesville, FL 32610, USA; okun@neurology.ufl.edu

References

1 **Okun MS**, McDonald WM, DeLong MR. Refractory nonmotor symptoms in male patients with Parkinson disease due to testosterone deficiency: a common unrecognized comorbidity. *Arch Neurol* 2002;**59**:807–11.
2 **Okun MS**, Walter BL, McDonald WM, *et al*. Beneficial effects of testosterone replacement for the non-motor symptoms of Parkinson disease. *Arch Neurol* 2002;**59**:1750–3.
3 **Hughes D**, Daniel SE, Kilfurd L, *et al*. Accuracy of clinical diagnosis in idiopathic Parkinson's disease: a clinicopathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;**55**:181–4.
4 **Olanow CW**, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. *Neurology* 2001;**56**(suppl 5):S1–88.
5 **Morley JE**, Charlton E, Patrick P, *et al*. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism* 2000;**49**:1239–42.
6 **Beck AT**, Beamesderfer A. Assessment of depression: the depression inventory. Psychological measurements in psychopharmacology. *Mod Probl Pharmacopsychiatry* 1974;**7**:151–69.
7 **Beck AT**. *The Beck depression inventory*. New York: Psychological Corporation, 1978.
8 **Harman SM**, Metter EJ, Tobin JD, *et al*. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab* 2001;**86**:724–31.
9 **Seidman SN**, Rabkin JG. Testosterone replacement therapy for hypogonadal men with SSRI-refractory depression. *J Affect Disord* 1998;**48**:157–61.

LBP-1c/CP2/LSF gene polymorphism and risk of sporadic Alzheimer's disease

The ε4 allele of apolipoprotein E (ApoE) accounts for an estimated 45–60% of the genetic risk for late onset sporadic Alzheimer's disease, suggesting that it may be possible to identify other genetic loci that could account for the remaining risk associated with this disease. Recently, a biallelic polymorphism (G/A) in the 3′ untranslated region (UTR) of the transcription factor LBP-1c/CP2/LSF (for brevity, CP2) has been implicated in Alzheimer's disease susceptibility, with the 3′-UTR A allele being associated with a reduction in the risk of sporadic Alzheimer's disease.[1–3] The CP2 gene is a plausible candidate for influencing Alzheimer's disease risk: it is located near the LDL receptor related protein gene within the Alzheimer's disease linkage region on chromosome 12; it controls the expression of several genes (α2 macroglobulin, glycogen synthase kinase-3β); and it interacts with different proteins (serum amyloid A3, interleukin 1α, tumour necrosis factor α, and Fe65 protein) and viruses (herpes simplex virus type I or human immunodeficiency virus) that are probably linked to Alzheimer's disease pathogenesis.[1 4] In the present study, we investigated the potential association of the CP2 polymorphism in a sample of sporadic early onset and late onset cases along with age and sex matched control subjects from southern Italy.

The Alzheimer's disease group consisted of 166 patients (62 men and 104 women) from the Apulia region with a mean (SD) actual age of 69.4 (10.3) years, including 95 patients with sporadic late onset disease (age at onset ⩾70 years; mean age 78.1 (4.9) years; 64 women and 31 men), and 71 patients with sporadic early onset disease (age at onset <70 years; mean age 63.7 (4.3) years; 50 women and 21 men). A clinical diagnosis of probable Alzheimer's disease was made according to the NINCDS/ADRDA criteria.[5] The age at