This week in *Neurology*®

Highlights of the January 27 issue

AMERICAN ACADEMY OF NEUROLOGY

Idiopathic intracranial hypertension in men

Idiopathic intracranial hypertension most commonly occurs in young, obese women. The authors found, however, that 10% of cases occur in men, and men have worse visual outcomes. This paper draws attention to the diagnosis of idiopathic intracranial hypertension in men, highlights the differences of the presentation in men, and explores the possibility that more aggressive interventions may be needed.

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Mutations in *GBA* are associated with familial Parkinson disease susceptibility and age at onset

The authors performed a comprehensive study of all glucocerebrosidase *(GBA)* exons in one patient with Parkinson disease from each of 96 families. These findings suggest that *GBA* is a susceptibility gene for familial Parkinson disease and patients with *GBA* variants have an earlier age at onset than Parkinson disease patients without *GBA* variants.

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TP53 codon 72 polymorphism is associated with age at onset of glioblastoma

The authors used blood samples from 254 patients with glioblastoma and 238 healthy controls. They found that pro variant on TP53 codon 72 is associated with early-onset glioblastoma and a higher rate of somatic TP53 mutation.

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Biochemical indicators of vitamin B_{12} and folate insufficiency and cognitive decline

This study shows a faster rate of cognitive decline in patients with high concentrations of methylmalonic acid over a 6-year interval. However, high serum concentrations of vitamin B_{12} were associated with a slower than expected rate of cognitive decline.

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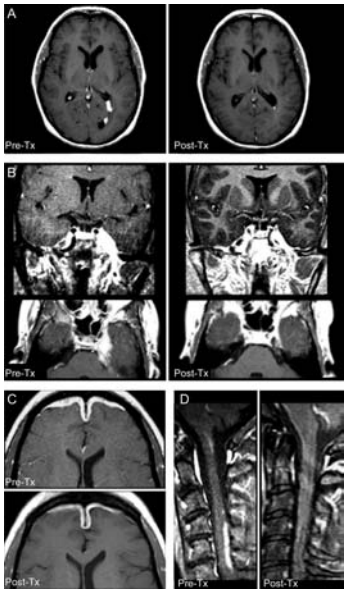

Treatment of CNS sarcoidosis with infliximab and mycophenolate mofetil

Sarcoidosis of the CNS is notoriously difficult to treat and tends to relapse during corticosteroid taper. This study reports on the successful treatment of a series of patients with neurosarcoidosis that was refractory to conventional immunosuppressant agents, with a combination of infliximab and mycophenolate mofetil.

See p. 337

Treatment of intractable chronic cluster headache by occipital nerve stimulation in 14 patients

The article suggests that some patients with otherwise unmanageable chronic cluster headache may now have a relatively noninvasive treatment option. These data provide medium-term follow-up in patients with medically intractable chronic cluster headache who have responded to occipital nerve stimulation.

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Factors associated with resistance to dementia despite high Alzheimer disease pathology

Understanding the factors that lead to greater reserve brain capacity may ultimately lead to prevention strategies. This paper supports the observation that various factors mediate whether individuals with Alzheimer disease pathology develop symptoms.

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Podcasts can be accessed at www.neurology.org

Idiopathic intracranial hypertension in men and the relationship to sleep apnea

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In this issue of *Neurology*®, Bruce et al.[1] use a retrospective chart review to study men who meet the modified Dandy criteria for idiopathic intracranial hypertension (IIH). This is the largest study to date of IIH in men and confirms the earlier suggestion that men with IIH are at greater risk for severe visual outcome than women.[2] The study, however, raises as many questions as it answers.

By design, retrospective studies tend to underestimate symptoms, signs, and disease associations, even in the best of hands. Bruce et al. report that 24% (16) of the men had sleep studies that met criteria for obstructive sleep apnea (OSA), but we do not know how many of the remaining 76% had negative polysomnography. Thus, the actual incidence of sleep apnea was likely underestimated. This is important because of the complex relationship between OSA and IIH.

A previous study[3] reported four men with OSA and papilledema. Nocturnal monitoring, performed in one patient, showed repeated episodes of marked intracranial pressure elevation associated with apnea and arterial oxygen desaturation. The authors concluded that intracranial hypertension with sleep apnea was due to episodic nocturnal hypoxemia and hypercarbia resulting in increased intracranial pressure (ICP) secondary to cerebral vasodilation and was sufficient to cause persistent disc edema even in the absence of elevated daytime intracranial pressure. Similar findings,[4,5] combined with the report of Bruce et al., suggest the rate of OSA in retrospective series of men with IIH is in the range of 24–37%. Since there are no published prospective investigations of IIH patients regarding the rate of sleep apnea in men, the true rate remains unknown.

To put the rates found by Bruce et al.[1] and others in perspective, one needs to know the rate in the population at large. In a random sample of 602 people between ages 30 and 60 years, the prevalence of sleep disordered breathing in the general population ranged from 4% to 9% for women and 9% to 24% for men, using a cutoff of an apnea-hypopnea score of 5 or greater. When daytime hypersomnolence was added, 4% of men and 2% of women met OSA syndrome criteria.[6] In addition, 30% of adults with a body mass index (BMI) of >30 kg/m^2 and 50% of those with a BMI >40 kg/m^2 have been reported to have OSA. While these figures suggest the association of sleep apnea and IIH could be related to chance alone, the lack of sleep studies in up to three quarters of men in this series argues against this.

Questions regarding the relationship between OSA and IIH remain. Is OSA a comorbidity with obesity or is it a cause of intracranial hypertension that persists through the day? If a cause, should we still consider patients with increased ICP and OSA to have IIH or should these patients be excluded? Recall that the modified Dandy criteria require that no other cause of intracranial pressure be present. If we assume that OSA is a cause of IIH, rather than a comorbidity, is there a plausible mechanism? Demonstrated collapse of the transverse sinus with intracranial hypertension provides us with such a mechanism.[7] Patients with OSA could well have enough intracranial hypertension while asleep to collapse the transverse sinuses, obstruct venous outflow, and have continued elevated pressure during the day.

Regardless of a possible causal relationship between sleep apnea and increased ICP, does the presence of sleep apnea perhaps affect the visual outcome? Considering that the mechanism for permanent visual loss in patients with papilledema is related to intraneuronal ischemia at the optic disc, the nocturnal oxygen desaturation, vasospasm, and other circulatory changes associated with sleep apnea could further compromise optic disc perfusion.

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Might OSA and not male gender thus account for the main finding in this study?

The authors conclude that male gender remains an independent risk factor for severe visual loss in at least one eye when adjusted for age, diagnosis of OSA, and headache as first sign of IIH. While their conclusions are clearly supported statistically, OSA was likely underdiagnosed. With prospective data collection, we might find that the reason for the poor visual outcome is OSA rather than being male.

The take-home message is that men who meet the Dandy criteria should be extensively evaluated for causes of intracranial hypertension, including obstructive sleep apnea. In spite of these questions, the importance of the article by Bruce et al. is that it establishes that men who the meet the Dandy criteria for IIH have worse visual outcomes than women with this diagnosis. It is prudent to follow visual function in these patients more closely and be more aggressive in treatment, including identification and vigorous treatment of OSA when present. Regardless of the mechanism, better visual outcomes should be observed in men with intracranial hypertension.

REFERENCES

1. Bruce BB, Kedar S, Van Stavern GP, et al. Idiopathic intracranial hypertension in men. Neurology 2009;72:304–309.
2. Digre KB, Corbett JJ. Pseudotumor cerebri in men. Arch Neurol 1988;45:866–872.
3. Purvin VA, Kawasaki A, Yee RD. Papilledema and OSA syndrome. Arch Ophthalmol 2000;118:1626–1630.
4. Marcus DM, Lynn J, Miller JJ, Chaudhary O, Thomas D, Chaudhary B. Sleep disorders: a risk factor for pseudotumor cerebri? J Neuro-Ophthalmol 2001;21:121–123.
5. Lee AG, Golnik K, Kardon R, Wall M, Eggenberger E, Yedavally S. Sleep apnea and intracranial hypertension in men. Ophthalmology 2002;109:482–485.
6. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230–1235.
7. Farb RI, Vanek I, Scott JN, et al. Idiopathic intracranial hypertension: the prevalence and morphology of sinovenous stenosis. Neurology 2003;60:1418–1424.

ACGME, test thyself!

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Everything is number.

—Pythagoras of Samos

In 1998, the Accreditation Council for Graduate Medical Education (ACGME) began an initiative to improve resident education to suit our current complex healthcare system. To this end, they defined six competence domains around which to focus educational assessment: 1) patient care, 2) medical knowledge, 3) practice-based learning and improvement, 4) interpersonal and communication skills, 5) professionalism, and 6) systems-based practice. The ACGME launched the Outcome Project in 2001. The stated goal of this project is to develop and implement a core competencies-based curriculum for medical education and to provide outcomes performance data to drive evaluation and improvement of medical education.[1] These performance data will play an increasing role as criteria for accreditation. The plan is for accreditation to move away from the evaluation of the potential to educate—that is, the structure and process components of education—and toward the evaluation of actual educational accomplishments—that is, outcomes.[2] The successful achievement of these goals should provide us with the information and organizational structure to improve the quality of graduate medical education. However, success will depend on flexible self-criticism within the ACGME, prompting it to adjust the design of the project.

In this issue of *Neurology*®, Schuh et al.[3] report the results of a survey of neurology residency program directors asked to comment on the current state of affairs. The findings are limited by the survey method, which lacks external confirmation, and by the scope of the questions, which did not seek judgments by the program directors on the effect of the project on education and patient care. However, the responses lead to some interesting conclusions. The demands on program directors have grown in recent years in large part as a result of the ambitious ACGME project, and it comes as no surprise that program directors report that they dedicate more to this work than their departments compensate in time, personnel support, and money. Based largely on differences of size and types of supporting facilities, programs have varying resources to provide explicit, curriculum-driven education in highly specialized areas of neurology and in nontraditional areas, such as medical ethics and practice management. Program directors welcome efforts by national organizations, such as the American Academy of Neurology, to fill such gaps with topic-focused curricula that can be adapted to use within their programs.

The survey asks mainly descriptive questions and avoids judgments about the value of the ACGME mandates. The one exception produces an interestingly negative response. Like their surgical colleagues, program directors do not feel that duty hour requirements have enhanced either patient care or resident education.[4,5] It is perhaps here, on the effects on patient care and education, that we should focus our attention.

The ACGME is moving into a new phase (Phase 3) of the Outcome Project during which it will expect programs to collect data on outcomes to show that the core competencies are being taught and learned and, one would hope, that they enhance education and patient care. Hearing the rumblings at the Consortium of Neurology Program Directors meetings loud and clear, I am afraid that the ACGME is getting ahead of itself. Phase 2 of the Outcome Project states the following as its goal: "Sharpening the focus and definition of the competencies and assessment tools."[2] This defining step of the project has not been a success. Although it has generated much anxiety among program directors, the ACGME has thus far failed to focus and define the core competencies and their assessment in a way that points to clear and practical actions for program directors. The six competencies are too diffuse and overlapping to be clearly isolated in a way that allows for meaningful measurement. This does not mean that they are not valuable. It simply acknowledges that they represent

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desirable components of the medical culture that span all practice, and in their complexity they remain hard to reduce to a simple score or number on a Likert scale, a number that is in fact deceptively full of biases and difficult to interpret.[6] There is an irony of self-reference here. Those holding the programs accountable are not holding themselves equally accountable. The debate between the ACGME and program directors has never been fully engaged, largely because the accrediting function of the ACGME places program directors in a weak position to oppose the ACGME. There is also little prospect of help from institutional GMEs that are intent on compliance, not dissent.

It is time for the ACGME to step back from the approach of mandating the fulfillment of vague directives. It should clarify its mission to determine what parameters are meaningfully measurable and which among these they wish to measure. These should then be made as explicit as possible along with recommended means of measurement and evaluation. The ACGME further needs to recognize which aspects of medical education, desirable though they may be, are best left in the category of medical culture, to be encouraged but not measured with unproven methods. Perhaps Pythagoras should reconsider: not quite everything is number.

REFERENCES

1. Swing S. The ACGME outcome project: retrospective and prospective. Med Teach 2007;29:648–654.
2. Outcome Project: enhancing residency education through outcomes assessment. Available at: www.acgme.org/outcome. Accessed December 14, 2008.
3. Schuh LA, Adair JC, Drogan O, Kissela BM, Morgenlander JC, Corboy JR. Neurology residency training in the new millennium. Neurology 2009;72:e15–e20.
4. Cohen-Gadol AA, Piepgras DG, Krishnamurthy S, Fessler RD. Resident duty hours reform: results of a national survey of the program directors and residents in neurosurgery training programs. Neurosurgery 2005;56:398–403.
5. Irani J, Mello MM, Ashley SW, et al. Surgical residents' perception of the effects of the ACGME duty hour requirements: 1 year after implementation. Surgery 2005;138:246–253.
6. Dawis R. Scale construction. J Couns Psychol 1987;34:481–489.

Idiopathic intracranial hypertension in men

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ABSTRACT

Objective: To compare the characteristics of idiopathic intracranial hypertension (IIH) in men vs women in a multicenter study.

Methods: Medical records of all consecutive patients with definite IIH seen at three university hospitals were reviewed. Demographics, associated factors, and visual function at presentation and follow-up were collected. Patients were divided into two groups based on sex for statistical comparisons.

Results: We included 721 consecutive patients, including 66 men (9%) and 655 women (91%). Men were more likely to have sleep apnea (24% vs 4%, $p < 0.001$) and were older (37 vs 28 years, $p = 0.02$). As their first symptom of IIH, men were less likely to report headache (55% vs 75%, $p < 0.001$) but more likely to report visual disturbances (35% vs 20%, $p = 0.005$). Men continued to have less headache (79% vs 89%, $p = 0.01$) at initial neuro-ophthalmologic assessment. Visual acuity and visual fields at presentation and last follow-up were significantly worse among men. The relative risk of severe visual loss for men compared with women was 2.1 (95% CI 1.4–3.3, $p = 0.002$) for at least one eye and 2.1 (95% CI 1.1–3.7, $p = 0.03$) for both eyes. Logistic regression supported sex as an independent risk factor for severe visual loss.

Conclusion: Men with idiopathic intracranial hypertension (IIH) are twice as likely as women to develop severe visual loss. Men and women have different symptom profiles, which could represent differences in symptom expression or symptom thresholds between the sexes. Men with IIH likely need to be followed more closely regarding visual function because they may not reliably experience or report other symptoms of increased intracranial pressure. *Neurology*® 2009;72:304–309

GLOSSARY

BMI = body mass index; **HVF MD** = Humphrey visual field mean deviation; **IIH** = idiopathic intracranial hypertension; **MR** = magnetic resonance; **VA** = visual acuity.

Although idiopathic intracranial hypertension (IIH) typically occurs in young, obese women, it does occur in men. Prognosis in IIH is variable, with severe visual loss occurring in up to 10% of patients.[1] Although few series have specifically evaluated sex differences in IIH, it has been suggested that men with IIH may have more severe visual outcomes.[2,3] The purpose of this study was to compare the characteristics of IIH in men vs women.

METHODS

The study was approved by each participating university's institutional review board. All consecutive charts for patients given the diagnosis code of IIH or disk edema seen by the neuro-ophthalmology services at Emory University (1989–2007), University of Mississippi (1989–2007), and Wayne State University (2001–2007) were identified and reviewed. Only patients with definite IIH diagnosed according to the modified Dandy criteria were included: 1) signs and symptoms of increased intracranial

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pressure, 2) no localizing signs except abducens nerve palsy, 3) CSF opening pressure ≥ 25 cm with normal CSF composition, and 4) normal neuroimaging (ruling out venous sinus thrombosis).[4]

Although the study was a retrospective chart review, all patients had been evaluated in a standardized fashion by experienced neuro-ophthalmologists, including documentation of body habitus, blood pressure, and complete neuro-ophthalmic examination with formal visual fields, fundus photography, review of neuroimaging tests, and recording of factors associated with IIH. Demographic information regarding age, sex, and race were collected. Race was assessed by the judgment of the examiner based on patient appearance. Medication use (current and recent), the presence or absence of several associated factors (recent weight gain, known sleep apnea, anemia [hemoglobin <12 g/dL], systemic hypertension, endocrine disorders, and pregnancy), symptoms (headache, tinnitus, diplopia, and transient visual obscuration), Snellen visual acuity, formal visual fields (static perimetry using a Humphrey automated perimeter and kinetic perimetry using a Goldmann perimeter), and dilated ophthalmoscopic appearance were recorded. Medications considered possibly contributing included vitamin A preparations, minocycline, cyclosporine, doxycycline, tetracycline, and recent discontinuation of steroids. The contributing medications were grouped by their presence or absence in each patient for analysis. Although not all patients had a formal assessment of their weight and height, for those who did, body mass index was calculated for use in statistical analyses according to the World Health Organization body mass index (BMI) guidelines.[5] Prediagnosis duration of symptoms, CSF opening pressure, height, weight, medical treatments, surgical treatments, follow-up duration, and visual outcome were also recorded.

Snellen visual acuity was converted to logMAR visual acuity for analysis. Formal visual fields were systematically reviewed for all patients. All visual field defects, whether obtained with static or kinetic perimetry, were graded on a 1 to 4 scale as 1) normal, 2) enlargement of the blind spot, 3) nasal or temporal defect, or 4) diffusely constricted. In addition, mean deviations were recorded for those patients who underwent static automated perimetry. Papilledema was graded with the Frisén staging scheme[6] by systematic review of fundus photography: stage 0 defines a normal optic nerve head, and stage 5 defines severe papilledema. Severe visual loss in an eye was defined by the US criteria for legal blindness (best corrected visual acuity less than or equal to 20/200 or total central visual field less than 20 degrees) and assessed at the last available visit. Patients were divided into two groups based on sex for statistical comparisons.

All patients had definite IIH by the modified Dandy criteria, but two aspects of our population merit further mention. First, although all patients underwent a lumbar puncture that documented elevation of CSF opening pressure, the specific value was sometimes unavailable. Second, clinically appropriate neuroimaging was performed on all patients to rule out cerebral venous thrombosis. However, because the patient population is representative of an actual clinical practice, there were occasionally practical limitations to obtaining ideal imaging studies, such as body habitus preventing entry into imaging gantries and changes in the clinical usage of MRI and magnetic resonance (MR) venography over the study period.[7] MRIs were all reviewed at the time of diagnosis, and MR venography or CT venography was obtained when there was a question regarding possible cerebral venous thrombosis. Those patients who could not have MRI had head CT with contrast, often accompanied by CT venography.

Statistical analysis was performed with R: a language and environment for statistical computing (R Foundation for Statistical Computing, http://www.R-project.org). Continuous and ordinal variables were compared between groups using the Mann–Whitney U test. The Pearson χ^2 test with the Yates continuity correction or the Fisher exact test, as appropriate, was used to compare the frequency distribution of categorical variables between groups. These tests were two tailed, and significance was set at 5%. Univariate analyses for sex vs other factors were undertaken on the entire population and on patients older than 12 years of age at diagnosis. A multivariate logistic regression analysis was performed with the outcome of severe visual loss in at least one eye with sex, age, diagnosis of sleep apnea, and headache as first sign of IIH included as predictors.

RESULTS We included 721 patients in the study. Emory University contributed 486 patients (67%), University of Mississippi contributed 193 (27%), and Wayne State University contributed 42 (6%). There were 66 (9%) men and 655 (91%) women.

The table details the differences between men and women with IIH. Men were more likely than women to have a diagnosis of sleep apnea (24% vs 4%, $p < 0.001$). Men reported less headache than women as the initial symptom of IIH (55% vs 75%, $p < 0.001$) and at the first neuro-ophthalmology evaluation (79% vs 89%, $p = 0.01$). Men were more likely than women to report visual changes as their first symptom of IIH (35% vs 20%, $p = 0.004$). Tinnitus was less frequently reported by men at first neuro-ophthalmology evaluation (26% vs 38%, $p = 0.05$).

MRI was obtained in 92% of all included patients. Those who were unable to undergo MRI had a head CT with contrast, often with CT venography. MR venography or CT venography was obtained in 34% of women and 26% of men ($p = 0.17$).

Men had significantly worse visual acuities and visual fields than women, at both initial and final evaluations (table). The relative risk of severe visual loss for men vs women was 2.1 (95% CI 1.4–3.3, $p = 0.002$) for one eye and 2.1 (95% CI 1.1–3.7, $p = 0.03$) for both eyes.

Subset analyses were performed on all patients older than 12 years of age at diagnosis, consisting of 53 men (8%) and 616 women (92%). All differences reported above remained significant within this subset, but men were additionally found to be older than women at diagnosis (37 vs 28 years, $p = 0.02$).

Male sex remained an independent risk factor for severe visual loss in at least one eye when adjusted for age, diagnosis of sleep apnea, and headache as first sign of IIH (adjusted odds ratio 2.5, $p = 0.004$ vs unadjusted odds ratio 2.6, $p = 0.001$).

DISCUSSION We present the largest series of IIH patients reported in the literature. Our study found a 9% prevalence of IIH in men, thereby confirming that IIH in men is rare. The prevalence of IIH in men has been estimated to be between 6% and 50%

Table Demographics, risk factors, CSF opening pressure, treatment, symptoms, and examination of men and women with idiopathic intracranial hypertension

	Women, n = 655		Men, n = 66		
	n or median	% or range	n or median	% or range	*p* Value
Demographics/risk factors					
Age, y (n = 719)	28	(2–67)	28	(2–65)	0.93
Black	311	(48%)	28	(42%)	0.41
Contributing medications	59	(9%)	2	(3%)	0.11
Sleep apnea	25	(4%)	16	(24%)	<0.001
Anemia	56	(9%)	3	(5%)	0.35
Endocrine disorder	83	(13%)	9	(14%)	0.82
Hypertension	140	(21%)	16	(24%)	0.59
Prediagnosis duration of symptoms, wk (n = 635)	6	(0–500)	4	(0–100)	0.10
Follow-up duration, wk (n = 678)	16	(0–592)	12.5	(0–168)	0.21
CSF opening pressure, cm CSF (n = 580)	37	(25–75)	37	(25–60)	0.67
Weight					
BMI, kg/m^2 (n = 487)	37.4	(12.4–83.6)	33.2	(17–73.1)	0.32
Recent weight gain	153	(23%)	9	(14%)	0.07
Amount of recent weight gain, kg (n = 136)	30	(5–150)	30	(10–100)	0.63
Treatment					
Medication	605	(92%)	59	(89%)	0.39
Diet modification	350	(53%)	30	(46%)	0.22
No. of lumbar punctures (n = 717)	1	(1–30)	1	(1–7)	0.69
CSF shunting	104	(16%)	10	(15%)	0.88
Repeat CSF shunting	45	(7%)	4	(6%)	1.00
Optic nerve sheath fenestration	97	(15%)	14	(21%)	0.17
Symptoms					
Initial symptom of IIH					
Headache	494	(75%)	36	(55%)	<0.001
Vision changes	130	(20%)	23	(35%)	0.004
Transient visual obscurations	72	(11%)	7	(11%)	0.92
Diplopia	32	(5%)	5	(8%)	0.37
Tinnitus	40	(6%)	2	(3%)	0.42
None	42	(6%)	8	(12%)	0.08
At first neuro-ophthalmology visit					
Headache	583	(89%)	52	(79%)	0.01
Transient visual obscurations	251	(38%)	18	(27%)	0.08
Diplopia	145	(22%)	16	(24%)	0.7
Tinnitus	250	(38%)	17	(26%)	0.05
Examination					
Papilledema, first visit (n = 618)	3	(0–5)	3	(0–5)	0.93
Papilledema, last visit (n = 658)	0	(0–5)	0	(0–3)	0.49
Visual field grade, first visit (n = 599)	2	(1–4)	2.8	(1–4)	0.006
Visual field grade, last visit (n = 631)	2	(1–4)	2	(1–4)	0.06
HVF MD, first visit (n = 422)	5	(0–33.5)	7.7	(1.1–33.5)	0.008
HVF MD, last visit (n = 490)	3.7	(0–33.1)	4.7	(1.1–31.2)	0.02
VA logMAR, first visit (n = 678)	0	(−0.3 to 6.9)	0.2	(−0.3 to 6.9)	<0.001
VA logMAR, last visit (n = 662)	0	(−0.3 to 6.9)	0.2	(−0.3 to 4.6)	0.002

BMI = body mass index; IIH = idiopathic intracranial hypertension; HVF MD = Humphrey visual field mean deviation; VA = visual acuity.

by prior studies,[2] but when one considers only studies applying modern neuroimaging to more than 50 IIH patients,[3,8-13] the prevalence range is 8% to 19%. This suggests that older studies may have included men with mimickers of IIH that are more difficult to diagnose without advanced neuroimaging (e.g., venous sinus thrombosis, dural arteriovenous malformations). Our study of IIH in men has the highest rate of MRI reported in the literature (>90%), making it less likely that we included patients with these conditions.

The most important finding of our study is that men were two times more likely than women to have severe visual loss in one or both eyes. Although sex has been previously suspected to be an important risk factor for visual loss in IIH, only two studies have specifically compared men vs women with IIH.[2,3] Although no significant association between male sex and visual loss in IIH has been demonstrated previously,[2,3,10,12,13] these studies were likely underpowered to find such an association, even if one was present.

Because visual loss in IIH is typically slow and insidious, the worse visual prognosis for men could be because men experience fewer nonvisual symptoms to bring them to medical attention early in the course of their disease. Indeed, men were found to report significantly less headache as both a first sign of IIH and at the initial neuro-ophthalmology visit. Instead, men were more likely to report that subjective visual changes were the heralding symptom of their illness. Men also reported less pulsatile tinnitus at initial neuro-ophthalmology evaluation, but this difference barely met our significance level and should be interpreted with caution. Further caution is warranted because higher symptom rates have been found in prospective studies and may suggest limitations in our retrospective data collection.[13,14] However, because our male and female patients were collected in a similar fashion and compared internally, there is no reason to specifically suspect bias to be the cause of the differences found. These symptom differences could suggest that IIH represents a different clinical entity in men and women. However, we believe it more likely represents a difference in headache thresholds for men and women. This is supported by several observations. First, migraine and tension-type headache are reported much more frequently by women than by men.[15,16] Second, women seem to have greater temporal summation of noxious mechanical stimuli than men do.[17] One could hypothesize from this observation that different responses to a constantly applied stimulus, such as chronically elevated intracranial pressure, may partially account for the sex headache differences in IIH. Finally, men are less likely than nonpregnant women to have post–dural puncture headaches.[18] This is particularly interesting because low-CSF-pressure and high-CSF-pressure headaches likely share a common mechanism, i.e., mechanical deformation of the meninges.

It is also possible that there were sex differences in other factors that have been previously associated with visual loss in IIH, such as degree of obesity, hypertension, recent weight gain, anemia, race, CSF opening pressure, sleep apnea, and older age.[2,8,13,19-24] Regarding obesity, one case–control study comparing 29 men with IIH to both women with IIH and normal men[2] found no differences between the men and women with IIH, but men with IIH were more obese than the age-matched control men. In another study comparing the characteristics of 18 men with IIH to 116 women with IIH,[3] men were less likely to be "significantly overweight" compared to women with IIH, but BMI was not used in the analyses. Among our 487 patients (67%) for whom BMI was available, no difference was found between the BMI of men and women with IIH. It is likely that studies that have suggested that obesity does not play a major role in the development of IIH in men were confounded by two problems: 1) inclusion of men with a different disease because of lack of adequate neuroimaging, and 2) the lack of precise anthropometric data (e.g., BMI), instead relying on weight only or the examiner's assessment of weight status.

Although some previous studies have suggested that systemic hypertension may be a poor prognostic indicator,[2,13] it was not found to be a significant factor in our study with regard to blindness. Because many of the patients in our study were treated hypertensives, this relationship may have been masked. In addition, we considered hypertension only by its presence or absence and not by a numerical value such as mean arterial pressure. This also reduces the power of finding a potentially significant relationship in this study.

We did find that men with IIH had a higher rate of diagnosed sleep apnea than women did. Epidemiologic studies have found a male-to-female ratio of sleep apnea of 5 to 8:1 in sleep clinics, whereas population-based studies have found a lower ratio of 2 to 3:1.[25] These observations suggest that although sleep apnea is likely more common in men in general, it may be underdiagnosed in women. The relationship between sleep apnea and IIH remains unclear. It is established that sleep apnea can cause nocturnal elevations in intracranial pressure that can lead to the development of papilledema.[26,27] However, there is debate about whether sleep apnea is causal or merely a comorbidity among patients whose

daytime intracranial pressure remains elevated.[28-31] Because of the retrospective nature of this study, we do not know which patients underwent sleep studies but did not have sleep apnea, and thus we are unable to further address this interesting mechanistic question. Regardless, because of the possible association of sleep apnea with worse visual outcome in IIH,[19] this relationship merits further study.

Excluding our younger, prepubertal patients, we also found that men were significantly older than women with IIH by nearly a decade. This has been observed in other studies of IIH in men but did not reach significance.[2,3] The fact that there is no clear sex predilection for IIH among younger children has been observed previously.[32,33] Together, these findings suggest that IIH has a bimodal distribution in male patients, with peaks during school age and middle age.

This predilection of IIH for women in their childbearing years supports a potential role of hormonal influences in the development of this disorder. However, if hormonal influences were directly responsible for the disorder, we would expect a correlation between development and severity of disease. Instead, IIH follows a paradoxical pattern similar to that of autoimmune disease, where women are affected disproportionately but men are affected more severely.[34] Because of the retrospective nature of this study, we do not have data on several potentially pertinent aspects of our male patients (e.g., history of autoimmune disease, use of anabolic steroids, history of sterility or impotence, central vs peripheral obesity), but we believe that these factors merit further study and may lend insight into the development and course of IIH and other similar disorders.

There were no differences between our men and women with IIH with regard to recent weight gain, anemia, race, or CSF opening pressure. After accounting for the differences in sleep apnea, headache, and age discussed above, sex remained an independent risk factor for poor visual outcome in IIH, increasing the odds of severe visual loss twofold.

Finally, we considered the possibility that the worse visual outcomes among men in our study could have been related to delayed diagnosis. However, median time from first symptom onset to diagnosis of IIH was 2 weeks shorter for men compared with women. Another study of IIH in men[3] also found that men were diagnosed earlier after first symptoms than women were (14 vs 28 weeks). However, because men were more likely to have visual complaints as their first symptoms and more likely to have significant visual loss at presentation compared with women, men may have been first examined by eye care professionals more frequently. This would likely lead to the discovery of disk edema and the correct diagnosis, but after chronic papilledema had already led to visual loss. Conversely, the longer time to diagnosis for women suggests that they were treated for primary headache disorders before their disease was recognized, which emphasizes the importance of examining the ocular fundi of all patients with headache.

The main limitation of our study is its retrospective nature, which requires a prudent interpretation of our findings, especially with regard to symptoms. However, all of our patients were systematically evaluated by experienced neuro-ophthalmologists, and we have no reason to believe that our evaluations of men and women differed in such a way to introduce bias. Another limitation of the study was the treatment of visual field data using only a four-point scale. While this was able to show that visual fields were worse among men than women, it does not provide the opportunity for a more refined interpretation of the nature of these visual field differences. Although one should remain mindful of these limitations, our findings that men with IIH frequently have substantial visual impairment at presentation and may report nonvisual symptoms less often than women do suggest that men with IIH likely require more frequent monitoring and more aggressive treatment.

AUTHOR CONTRIBUTIONS

Statistical analysis was performed by B.B.B.

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REFERENCES

1. Ball AK, Clarke CE. Idiopathic intracranial hypertension. Lancet Neurol 2006;5:433–442.
2. Digre KB, Corbett JJ. Pseudotumor cerebri in men. Arch Neurol 1988;45:866–872.
3. Kesler A, Goldhammer Y, Gadoth N. Do men with pseudomotor cerebri share the same characteristics as women? A retrospective review of 141 cases. J Neuroophthalmol 2001;21:15–17.
4. Friedman DI, Jacobson DM. Diagnostic criteria for idiopathic intracranial hypertension. Neurology 2002;59:1492–1495.
5. Physical status: the use and interpretation of anthropometry: report of a WHO expert committee. WHO Tech Rep Ser 1995;854:1–452.
6. Frisén L. Swelling of the optic nerve head: a staging scheme. J Neurol Neurosurg Psychiatry 1982;45:13–18.
7. Biousse V, Ameri A, Bousser MG. Isolated intracranial hypertension as the only sign of cerebral venous thrombosis. Neurology 1999;53:1537–1542.
8. Corbett JJ, Savino PJ, Thompson HS, et al. Visual loss in pseudotumor cerebri: follow-up of 57 patients from five to 41 years and a profile of 14 patients with permanent severe visual loss. Arch Neurol 1982;39:461–474.

9. Durcan FJ, Corbett JJ, Wall M. The incidence of pseudotumor cerebri: population studies in Iowa and Louisiana. Arch Neurol 1988;45:875–877.
10. Galvin JA, Van Stavern GP. Clinical characterization of idiopathic intracranial hypertension at the Detroit Medical Center. J Neurol Sci 2004;223:157–160.
11. Kesler A, Gadoth N. Epidemiology of idiopathic intracranial hypertension in Israel. J Neuroophthalmol 2001;21:12–14.
12. Mezaal M, Saadah M. Idiopathic intracranial hypertension in Dubai: nature and prognosis. Acta Neurol Scand 2005;112:298–302.
13. Wall M, George D. Idiopathic intracranial hypertension: a prospective study of 50 patients. Brain 1991;114:155–180.
14. Giuseffi V, Wall M, Siegel PZ, Rojas PB. Symptoms and disease associations in idiopathic intracranial hypertension (pseudotumor cerebri): a case-control study. Neurology 1991;41:239–244.
15. Schwartz BS, Stewart WF, Simon D, Lipton RB. Epidemiology of tension-type headache. JAMA 1998;279:381–383.
16. Silberstein SD. Headache and female hormones: what you need to know. Curr Opin Neurol 2001;14:323–333.
17. Sarlani E, Greenspan JD. Gender differences in temporal summation of mechanically evoked pain. Pain 2002;97:163–169.
18. Wu CL, Rowlingson AJ, Cohen SR, et al. Gender and post–dural puncture headache. Anesthesiology 2006;105:613–618.
19. Bruce BB, Preechawat P, Newman NJ, Lynn MJ, Biousse V. Racial differences in idiopathic intracranial hypertension. Neurology 2008;70:861–867.
20. Biousse V, Rucker JC, Vignal C, Crassard I, Katz BJ, Newman NJ. Anemia and papilledema. Am J Ophthalmol 2003;135:437–446.
21. Lee AG, Golnik K, Kardon R, Wall M, Eggenberger E, Yedavally S. Sleep apnea and intracranial hypertension in men. Ophthalmology 2002;109:482–485.
22. Orcutt JC, Page NG, Sanders MD. Factors affecting visual loss in benign intracranial hypertension. Ophthalmology 1984;91:1303–1312.
23. Radhakrishnan K, Thacker AK, Bohlaga NH, Maloo JC, Gerryo SE. Epidemiology of idiopathic intracranial hypertension: a prospective and case-control study. J Neurol Sci 1993;116:18–28.
24. Thambisetty M, Lavin PJ, Newman NJ, Biousse V. Fulminant idiopathic intracranial hypertension. Neurology 2007;68:229–232.
25. Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc 2008;5:136–143.
26. Purvin VA, Kawasaki A, Yee RD. Papilledema and obstructive sleep apnea syndrome. Arch Ophthalmol 2000;118:1626–1630.
27. Sugita Y, Iijima S, Teshima Y, et al. Marked episodic elevation of cerebrospinal fluid pressure during nocturnal sleep in patients with sleep apnea hypersomnia syndrome. Electroencephalogr Clin Neurophysiol 1985;60:214–219.
28. Corbett JJ. "Pseudotumor cerebri" by any other name. Arch Ophthalmol 2000;118:1685.
29. Marcus DM, Lynn J, Miller JJ, Chaudhary O, Thomas D, Chaudhary B. Sleep disorders: a risk factor for pseudotumor cerebri? J Neuroophthalmol 2001;21:121–123.
30. Kirkpatrick PJ, Meyer T, Sarkies N, Pickard JD, Whitehouse H, Smielewski P. Papilloedema and visual failure in a patient with nocturnal hypoventilation. J Neurol Neurosurg Psychiatry 1994;57:1546–1547.
31. Wolin MJ, Brannon WL. Disk edema in an overweight woman. Surv Ophthalmol 1995;39:307–314.
32. Balcer LJ, Liu GT, Forman S, et al. Idiopathic intracranial hypertension: relation of age and obesity in children. Neurology 1999;52:870–872.
33. Lessell S. Pediatric pseudotumor cerebri (idiopathic intracranial hypertension). Surv Ophthalmol 1992;37:155–166.
34. Gleicher N, Barad DH. Gender as risk factor for autoimmune diseases. J Autoimmun 2007;28:1–6.

Mutations in *GBA* are associated with familial Parkinson disease susceptibility and age at onset

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ABSTRACT

Objective: To characterize sequence variation within the glucocerebrosidase (*GBA*) gene in a select subset of our sample of patients with familial Parkinson disease (PD) and then to test in our full sample whether these sequence variants increased the risk for PD and were associated with an earlier onset of disease.

Methods: We performed a comprehensive study of all *GBA* exons in one patient with PD from each of 96 PD families, selected based on the family-specific lod scores at the *GBA* locus. Identified *GBA* variants were subsequently screened in all 1325 PD cases from 566 multiplex PD families and in 359 controls.

Results: Nine different *GBA* variants, five previously reported, were identified in 21 of the 96 PD cases sequenced. Screening for these variants in the full sample identified 161 variant carriers (12.2%) in 99 different PD families. An unbiased estimate of the frequency of the five previously reported *GBA* variants in the familial PD sample was 12.6% and in the control sample was 5.3% (odds ratio 2.6; 95% confidence interval 1.5–4.4). Presence of a *GBA* variant was associated with an earlier age at onset ($p = 0.0001$). On average, those patients carrying a *GBA* variant had onset with PD 6.04 years earlier than those without a *GBA* variant.

Conclusions: This study suggests that *GBA* is a susceptibility gene for familial Parkinson disease (PD) and patients with *GBA* variants have an earlier age at onset than patients with PD without *GBA* variants. ***Neurology*® 2009;72:310–316**

GLOSSARY

CI = confidence interval; **GD** = Gaucher disease; **GDS** = Geriatric Depression Scale; **MMSE** = Mini-Mental State Examination; **NCRAD** = National Cell Repository for Alzheimer's Disease; **NPL** = nonparametric lod; **OR** = odds ratio; **PD** = Parkinson disease; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Parkinson disease (PD) is the second most common neurodegenerative disease after Alzheimer disease. Mutations in *SNCA*, *PRKN*, *DJ1*, and *PINK1* typically result in early onset PD[1,2] while mutations in *LRRK2* result in idiopathic PD with more typical, later onset.[3,4] These mutations result in disease in fewer than 5% of patients with PD.

Gaucher disease (GD) is an inherited deficiency of lysosomal glucocerebrosidase arising from mutations in the gene encoding glucosidase beta acid (*GBA*), more commonly known as glucocerebrosidase.[5-7] Over 200 different mutations have been identified. GD is most common in the Ashkenazi Jewish population. While patients with GD presenting with parkinsonian symptoms were reported as early as 1939, only recently has it been hypothesized that a deficiency of glucocerebrosidase might contribute to an increased susceptibility to parkinsonism.[8,9] In a recent study, *GBA* variants were found in 21% of subjects with PD, a much higher

Supplemental data at www.neurology.org

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Table 1 Patients with Parkinson disease (PD) and control sample demographics

Source	Type	No.	Mean age at onset/ examination, y (range)	% Male
PROGENI (samples reported to have PD)	Cases	1,325	60.9 (15-89)	58.0
PROGENI (Caucasian non-Hispanic with verified PD)	Cases	737	61.9 (15-84)	59.8
PROGENI-CARES	Controls	46	68.4 (55-82)	19.6
National Cell Repository for Alzheimer's Disease	Controls	44	76.9 (58-92)	43.2
NINDS Human Genetics Resource Center (Coriell)	Controls	269	69.5 (55-88)	48.0

NINDS = National Institute of Neurological Disorders and Stroke.

estimate than would be expected based on the carrier frequency of GD in the general population.[10] In addition, *GBA* variants were more frequent among younger patients.

Subsequent screenings of patients with PD has yielded contradictory results regarding the association of *GBA* in PD.[10-23] In one study of Ashkenazi Jewish patients with PD, *GBA* variants were more frequently found in patients as compared with controls.[11] A large study of both Jewish and non-Jewish samples found an association between *GBA* mutations and PD in the Jewish group only.[15] Chinese patients with PD from Singapore demonstrated a significant association with *GBA*,[21] whereas a similar study of Chinese patients from Taiwan did not.[20] A survey of Italian patients with PD for the N370S and L444P mutations found a significant association of these variants with PD,[22] while a Norwegian sample showed comparable frequencies of these two mutations in patients with PD and controls.[17] Most recently, a study of Portuguese patients with PD detected a significant increase in *GBA* variants in patients as compared to controls.[23] In some studies, patients with PD harboring *GBA* variants had earlier age at disease onset.[12,15,19,21] Whether the discrepant results regarding the association of *GBA* with disease and age at onset result from true ethnic differences in *GBA* variant frequencies or from differences in the scope of the studies (i.e., only screening for certain variants as opposed to sequencing the entire coding region) remains to be determined.

Of the studies previously reported, none has examined the relationship of *GBA* to PD susceptibility in a largely familial cohort.[10-23] The goals of this study were to characterize sequence variation within *GBA* in a select subset of our large sample of patients with familial PD and then to test in the entire sample whether these sequence variants increased the risk for PD or were associated with an earlier onset of disease.

METHODS

Subjects. A total of 1,325 individuals with PD from 566 multiplex families were ascertained through a pair of siblings, both of whom were reported to have PD (PROGENI study). At the time of these analyses, 1325 individuals with PD from 566 multiplex PD families had been recruited. All available affected individuals were seen by a movement disorder specialist at one of 59 Parkinson Study Group sites located throughout North America (table 1). Each participant completed a uniform clinical assessment that included the Unified Parkinson's Disease Rating Scale (UPDRS) Parts II (Activities of Daily Living) and III (Motor Exam),[24,25] Schwab & England score,[26] Hoehn & Yahr stage,[27] the Mini-Mental State Examination (MMSE),[28] the Geriatric Depression Scale (GDS),[29] and the Blessed Functional Activity Scale (Blessed).[30] In addition, a diagnostic checklist was used to classify individuals as having either verified PD (65%) or nonverified PD (35%).[31] Peripheral blood was obtained after completion of appropriate written informed consent approved by each individual institution's institutional review board.

Microsatellite markers closest to the *GBA* locus (D1S252, D1S498, D1S484, D1S2878) genotyped as part of a previous 10 cM genome screen[31-33] were used to calculate a family-specific nonparametric lod (NPL) score and rank families based on their evidence of linkage to the *GBA* region. One affected individual from each of the 96 families with the highest NPL scores was selected for *GBA* sequencing.

The control sample consisted of 359 neurologically normal non-Hispanic Caucasians who provided appropriate written informed consent (see table 1). The control samples were obtained from three different sources: the National Cell Repository for Alzheimer's Disease (NCRAD), the National Institute of Neurological Disorders and Stroke Human Genetics Resource Center at the Coriell Cell Repositories (Camden, NJ; DNA panels NDPT002, NDPT006, NDPT009) and controls recruited as part of an ongoing PD study at Indiana University (PROGENI-CARES).[34]

Molecular genetic analysis. PCR and sequencing primers were designed using the chromosome 1 genomic contig sequence NT_029419 enabling PCR/sequencing of all 11 coding exons and corresponding intron/exon boundaries of *GBA* (table e-1 on the *Neurology*® Web site at www.neurology.org). Primers were designed enabling preferential amplification of *GBA* over the *GBA* pseudogene also on chromosome 1. PCR products were purified and sequenced as previously described.[34]

TaqMan allelic-discrimination assays (Applied Biosystems, Foster City, CA) were developed to screen all 1,325 PD cases and 359 controls for the variants identified in the 96 sequenced samples (except L444P, A456P, V460V) as previously described.[34,35] To screen for the L444P variant, exon 11 amplification products were digested to completion with *Hpa*II (New England Biolabs, Beverly, MA) to assay for the L444P variant (gain of *Hpa*II site). Digestion products were electrophoresed through 4% Metaphor Agarose (Cambrex, Rockland, ME). To screen for the Rec*Nci*I recombinant allele carrying variants

Table 2 *GBA* variants identified by sequencing in 96 familial patients with Parkinson disease (PD) and number of families identified to carry each by screening the full sample

Exon	Nucleotide change	Amino acid change	References	No. of families with variant*
7	IVS6 589-2A>G		This report	1
8	c. 902 G>A	R262H	This report	1
9	c.1026 A>G	K303K	This report	1
9	c.1093 G>A	E326K	10, 15	44
9	c.1223 C>T	T369M	12, 15	19
10	c. 1226 A>G	N370S	8, 10–15, 17, 19	19
11	c.1448 T>C	L444P	8, 10–15, 17, 19–21	9
11	IVS10 1389-3C>G		This report	1
11	c. 1448 T>C	Rec*Nci*I (L444P+A456P+V60V)	12, 13, 15, 21	4
	c. 1483 G>C			
	c. 1497 G>C			

*Screened in the full sample of 1,325 PD cases from 566 multiplex PD families.

A456P and V460V, PCR primers were synthesized as described previously.[13] The gene-specific forward primer (5′-ggaaccatgattccctatcttc-3′) and the *GBA* pseudogene-specific reverse primer (5′-gtttaggacgaccacaacagg-3′) were used in a multiplex PCR reaction with an invariant primer set. The PCR products were electrophoresed through 2% agarose (Invitrogen, Carlsbad, CA) for detection of the Rec*Nci*I recombinant allele PCR fragment. Presence of the Rec*Nci*I recombinant allele was confirmed using long range PCR and sequencing of the entire *GBA* gene. Briefly, 200 ng of genomic DNA was amplified using the Invitrogen Elongase Enzyme Mix (Invitrogen, Carlsbad, CA) and primers 5′-cccattctccatgcaaatctgtgt-3′ (forward) and 5′-ccggaaccagatcctatctgtgc-3′ (reverse). Long range PCR products were purified and sequenced as above.

Statistical analysis. Statistical analyses were limited to the subset of the PD sample that met the strictest diagnostic criteria of verified PD.[31] This analytic sample consisted of 737 non-Hispanic, Caucasian individuals from 450 families (see table 1) and excluded those patients known to harbor a causative PD mutation (a single *LRRK2* mutation or 2 *PRKN* mutations).

Two hypotheses were tested. The first was that presence of a *GBA* variant increased the risk of PD. A logistic model was employed with affection status as the dependent variable and presence or absence of a *GBA* variant as the independent variable (0 or 1). Age at examination and gender were included as covariates in the initial model; however, neither affected the magnitude or significance of the odds ratios (ORs) and were dropped from the final model. The second hypothesis was that those inheriting a *GBA* variant have earlier age at PD onset. A linear regression model was fitted with age at onset as the dependent variable and the presence or absence of a *GBA* variant as the independent variable. Education, gender, and smoking were considered as possible covariates; however, all were found to be nonsignificant and were dropped from the final model. Linear and logistic regression models were also used to test whether other measures relevant to PD (i.e., UPDRS subscores, MMSE, GDS, Hoehn & Yahr stage) differed based on the presence or absence of a *GBA* variant.

All analyses were carried out using SAS software (release 9.13; SAS Institute, Cary, NC). Our analytic sample consisted of families with multiple patients with PD. To ensure an unbiased analysis of the study hypotheses when using a sample of related individuals, we employed resampling techniques. Specifically, a single individual was sampled at random from each of the families. This was repeated 50,000 times, and common resampling techniques (bootstrapping) were employed to obtain a representative value. The median bootstrapped statistic was determined and the corresponding p values are reported for the tests of the two hypotheses.

RESULTS Nine variants were identified by sequencing the entire coding region of *GBA* in 96 patients with PD (table 2). Four of the detected sequence variants were novel while the remaining five had been previously identified in patients with PD. The four novel variants were each found in additional affected family members of the PD subject in whom the variant was initially found. However, screening of all available PD cases did not identify the four novel variants in any additional families. Three of the variants (IVS6 589-2A>G, R262H, IVS10 1389-3C>G) were not identified in any of the control samples, making the estimated frequency of each <0.002 in the neurologically normal population. The frequency of the remaining novel variant, K303K, was not evaluated in the control samples as the designed TaqMan allelic discrimination assay failed. The remaining five variants had been previously reported in patients with PD and GD, as well as controls.[8,10-15,17,19-21] An unbiased estimate (using resampling techniques as described in Methods) of the frequency of the five previously reported *GBA* variants in the subset of the familial PD sample that met our strictest diagnostic criteria of verified PD was 12.6% and in the control sample was 5.3% (table 3). The mean age at onset of the patients with PD harboring a *GBA* variant was 56.8 years (median: 58, range: 30–79).

The presence of a previously described *GBA* variant significantly increased the risk for PD; 12.6% of verified PD cases carried a *GBA* mutation (permuted one per family as described in Methods), as compared with 5.3% of controls (OR 2.6, 95% confidence interval [CI] 1.5–4.4) (table 3). The analysis of individual variants showed nonsignificant ORs ranging from 1.7 (95% C.I. 0.4–6.8) for the N370S variant to 2.8 (95% C.I. 0.3–25.8) for the Rec*Nci*I recombinant allele variant.

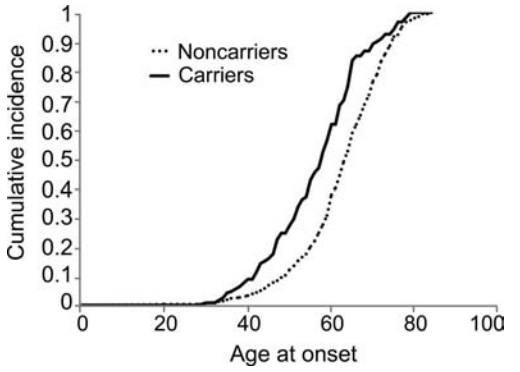
Presence of a *GBA* variant was also associated with an earlier age at onset ($p = 0.0001$) (table 4). PD cases carrying a *GBA* variant were more likely to have onset ≤50 years as compared to those without a *GBA* variant ($p = 0.0004$). Among those with early onset disease, there was no difference in age at onset between the *GBA* variant carriers and the noncarriers; however, among those with onset >50 years, those

Table 3 Odds ratios and proportions of cases and controls with a previously identified *GBA* variant permuted one per family

	Cases (n = 450), % carriers	Controls (n = 359), % carriers	OR (95% CI)
All *GBA* variants	12.6	5.3	2.6 (1.5–4.4)
E326K variants	6.2	3.1	2.1 (1.0–4.3)
T369M variants	2.3	1.1	2.1 (0.7–6.8)
N370S variants	1.4	0.8	1.7 (0.4–6.8)
L444P variants	1.9	0.0	Ø
A456P/V460V/L444P variants	0.8	0.3	2.8 (0.3–25.8)

Ø = OR cannot be calculated as all carriers were cases (divide by zero); Fisher exact test yields a *p* value of 0.01.
OR = odds ratio; CI = confidence interval.

Figure Cumulative incidence rates of Parkinson disease among carriers and noncarriers of *GBA* variants



with a *GBA* variant had earlier age at onset (61.59 years) as compared to late-onset cases without a *GBA* variant (65.37 years) ($p = 0.001$).

When a linear regression model was fitted to predict age at onset, presence of a *GBA* variant was associated with an earlier age at onset ($p = 0.0001$). On average, our model suggests that those patients carrying a *GBA* variant had onset with PD 6.04 years earlier than those without a *GBA* variant. The cumulative incidence of PD was higher in patients with *GBA* variants compared with noncarriers over nearly the entire age distribution (figure).

We also compared the clinical characteristics of the PD cases that carried a *GBA* variant with the PD cases that did not carry a *GBA* variant. There were no significant differences between *GBA* variant carriers and noncarriers for any of the clinical characteristics examined, including MMSE, UPDRS Parts II and III, Blessed, and Hoehn & Yahr (table 3).

Table 4 Comparison of clinical features of *GBA* variant carriers and noncarriers with a diagnosis of verified Parkinson disease

	Carriers	Noncarriers	*p* Value
No.	56.8*	393.2	
Male, %	58.9	59.2	0.56
Age at onset, y	56.8	62.8	0.0001
Early onset (≤50 y), %	63.3	37.8	0.0004
Duration of disease, y	9.6	8.3	0.15
Affected parent, %	35.3	28.3	0.25
Education, y	13.7	13.6	0.55
Depression (GDS)	9.9	9.0	0.25
MMSE	26.2	26.7	0.34
UPDRS Part II (motor)	28.6	27.7	0.49
UPDRS Part III (ADL)	14.4	13.6	0.36
Blessed Functionality	4.7	3.9	0.10
Schwab Examiner	74.9	77.9	0.22
Hoehn & Yahr stage	2.5	2.5	0.53

*To produce unbiased results, all values and statistics are permuted one per family, which leads to counts containing fractions.

DISCUSSION The goals of this study were to characterize sequence variation within *GBA* in a select subset of our larger sample of familial patients with PD and to test in the larger sample whether these sequence variants increased the risk for PD and were associated with an earlier onset of disease. We identified four novel variants and five previously reported variants. In our sample, a subject was 2.6 times more likely to develop PD if they carried one of the five previously identified *GBA* variants (table 3). Furthermore, presence of a *GBA* variant was associated with an earlier onset of disease. Our results replicate the association of *GBA* with PD reported in other studies[10-23]; however, we extend the association to include later onset patients with PD as well as familial disease.

Our screening for these nine variants in 1,325 affected individuals from 566 families represents the largest study to date of *GBA* variants in patients with PD and PD families. In total, *GBA* variants were detected in 161 patients (12.2%) from 99 different PD families (17.5%). The frequency observed in our sample is intermediate with that in a recent study that reported 16.9% of Jewish PD cases carried a *GBA* variant, while only 8% of non-Jewish PD cases carried a variant.[15] While the exact percentage of our sample which is of Jewish ancestry is not known, it is likely less than 10%.

As we did not sequence any of our control samples, our statistical analyses included only the five previously published *GBA* variants to avoid any ascertainment bias. While the analysis for these five variants combined yielded an OR of 2.6 (95% CI 1.5–4.4), individual ORs for each of the variants were not significant (table 3). For the N370S variant in our patients, the OR of 1.7 (95% CI 0.4–6.8) was

less than the 5.6 (95% CI 1.3–24.3) in a recent report[15]; however, the CIs do overlap. This difference is likely due to the large number of Jewish PD cases (179/278) included in their study and the high frequency of the N370S variant in that population, in general. No other study has reported ORs for individual *GBA* variants as we have in this study. Since the variant observed most often in our verified patients with PD, E326K (table 3), has been described as a "mild" mutation or modifier allele,[34,35] the analyses were also performed without those patients carrying this variant. Even when those patients are removed, the frequency of *GBA* variants in the cases remains greater than in the controls ($p = 0.002$) suggesting that the GBA effect is not solely due to E326K. In our study, a single patient not meeting our strictest diagnostic criteria of verified PD was shown to be homozygous for the E326K variant.

We have also demonstrated that those patients with PD carrying a *GBA* variant had onset with PD 6 years earlier than patients without a *GBA* variant. Among the patients with later onset disease (after age 50), those with a *GBA* variant had a significantly earlier age at onset (61.6 years) as compared to those without a *GBA* variant (65.4 years). However, the earlier age at onset in *GBA* variant carriers was not observed when limiting the analysis to those patients having earlier onset (≤ age 50). These results differ from those of a recent study that reported the presence of a *GBA* variant decreased age at onset by nearly 2 years among patients with early onset PD.[15] Analysis of the later onset PD cases in this same study did not detect a significantly earlier age at onset in carriers of a *GBA* variant. It is unclear whether this results from a difference in the ethnicity of two sample populations studied or any bias in collection of the samples. When those with the E326K variant are removed from the analyses, patients with PD with a *GBA* variant continue to have earlier age at onset compared to those without a variant ($p = 0.008$).

Four novel variants were each identified in a single family. None of these variants have been reported in either patients with PD or GD, and none was identified in 359 normal control subjects. Two of the novel variants were intronic (IVS6 589-2A>G and IVS10 1389-3C>G), and their close proximity to the 3′ end of the intron (either −2 or −3 position) suggests that either could alter the splice donor site resulting in altered splicing of the *GBA* mRNA. One synonymous (K303K) and one nonsynonymous (R262H) variant were each identified in a single family. As the synonymous variant does not alter the amino acid sequence of glucocerebrosidase, it is not predicted to be pathogenic for either PD or GD. However, the possibility that the nucleotide substitution results in creation of either a cryptic splice donor or acceptor site cannot be ruled out. Any disease susceptibility attributable to the R262H variant could not be determined in this study. Thus, while none of these four *GBA* variants have been previously identified, each either alters or could potentially alter the glucocerebrosidase sequence and may contribute to disease pathogenesis.

In all, *GBA* variants were identified in 99 of 566 (17.5%) families. Discordance for *GBA* variant carrier status among affected individuals (both verified and nonverified PD) within the 99 families was common. Of the 99 *GBA* variant-carrying families, 63 demonstrated discordance for inheritance of the *GBA* variant among affected individuals. Among the discordant families, we compared age at onset between those PD cases who carried a *GBA* variant and those cases who did not. Those with a pathogenic variant (N370S, L444P, Rec*Nci*I) had a earlier age at onset ($p = 0.01$) than those without a variant (56.4 years vs 66.5 years). Interestingly, among the discordant families, carriers of a polymorphic variant (either E326K or T369M) also had lower age at onset than those without a variant (57.1 years vs 61.4 years; $p = 0.03$).

Our study is unique in that 96 unrelated familial patients with PD were selected for sequencing of the glucocerebrosidase gene based on their lod score in the *GBA* chromosomal region that exceeded 0.60. Previous reports focused primarily on sporadic or idiopathic PD except for that of Sato et al., for which 51% of patients with PD reported a positive family history.[13] Nine *GBA* variants were identified in 21 of the 96 patients, making the yield for this lod score strategy 21.9%. The nine *GBA* variants were only identified in 16.5% of the remaining 470 families. Thus, while linkage methods have very limited specificity for identifying causative mutations when a majority of the families in a study contain only a single affected sibling pair, the apparent increase in sensitivity illustrates that this is a helpful strategy for prioritizing which individuals to sequence in the evaluation of potential PD susceptibility genes.

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APPENDIX

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REFERENCES

1. Farrer MJ. Genetics of Parkinson disease: paradigm shifts and future prospects. Nat Rev Genet 2006;7:306–318.
2. Gasser T. Genetics of Parkinson's disease. Curr Opin Neurol 2005;18:363–369.
3. Zimprich A, Biskup S, Leitner P, et al. Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. Neuron 2004;44:601–607.
4. Paisan-Ruiz C, Jain S, Evans EW, et al. Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. Neuron 2004;44:595–600.
5. Sidransky E. Gaucher disease: complexity in a "simple" disorder. Mol Genet Metab 2004;83:6–15.
6. Butters TD. Gaucher disease. Curr Opin Chem Biol 2007; 11:412–418.
7. Germain DP. Gaucher's disease: a paradigm for interventional genetics. Clin Genet 2004;65:77–86.
8. Tayebi N, Walker J, Stubblefield B, et al. Gaucher disease with parkinsonian manifestations: does glucocerebrosidase deficiency contribute to a vulnerability to parkinsonism? Mol Genet Metab 2003;79:104–109.
9. Tayebi N, Callahan M, Madike V, et al. Gaucher disease and parkinsonism: a phenotypic and genotypic characterization. Mol Genet Metab 2001;73:313–321.
10. Lwin A, Orvisky E, Goker-Alpan O, LaMarca ME, Sidransky E. Glucocerebrosidase mutations in subjects with parkinsonism. Mol Genet Metab 2004;81:70–73.
11. Aharon-Peretz J, Rosenbaum H, Gershoni-Baruch R. Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews. N Engl J Med 2004; 351:1972–1977.
12. Eblan MJ, Nguyen J, Ziegler SG, et al. Glucocerebrosidase mutations are also found in subjects with early-onset parkinsonism from Venezuela. Mov Disord 2006;21:282–283.
13. Sato C, Morgan A, Lang AE, et al. Analysis of the glucocerebrosidase gene in Parkinson's disease. Mov Disord 2005; 20:367–370.
14. Clark LN, Nicolai A, Afridi S, et al. Pilot association study of the beta-glucocerebrosidase N370S allele and Parkinson's disease in subjects of Jewish ethnicity. Mov Disord 2005;20:100–103.
15. Clark LN, Ross BM, Wang Y, et al. Mutations in the glucocerebrosidase gene are associated with early-onset Parkinson disease. Neurology 2007;69:1270–1277.
16. Goker-Alpan O, Giasson BI, Eblan MJ, et al. Glucocerebrosidase mutations are an important risk factor for Lewy body disorders. Neurology 2006;67:908–910.
17. Toft M, Pielsticker L, Ross OA, Aasly JO, Farrer MJ. Glucocerebrosidase gene mutations and Parkinson disease in the Norwegian population. Neurology 2006;66:415–417.
18. Eblan MJ, Walker JM, Sidransky E. The glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews. N Engl J Med 2005;352:728–731.
19. Tan EK, Tong J, Fook-Chong S, et al. Glucocerebrosidase mutations and risk of Parkinson disease in Chinese patients. Arch Neurol 2007;64:1056–1058.
20. Ziegler SG, Eblan MJ, Gutti U, et al. Glucocerebrosidase mutations in Chinese subjects from Taiwan with sporadic Parkinson disease. Mol Genet Metab 2007;91:195–200.
21. Wu YR, Chen CM, Chao CY, et al. Glucocerebrosidase gene mutation is a risk factor for early onset of Parkinson disease among Taiwanese. J Neurol Neurosurg Psychiatry 2007;78:977–979.
22. De Marco EV, Annesi G, Tarantino P, et al. Glucocerebrosidase gene mutations are associated with Parkinson's disease in southern Italy. Mov Disord 2008;23:460–463.

23. Bras J, Paisan-Ruiz C, Guerreiro R, et al. Complete screening for glucocerebrosidase mutations in Parkinson disease patients from Portugal. Neurobiol Aging EPub 2007 Dec 19.
24. Fahn S, Elton R, Committee UD. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden C, Goldstein M, eds. Recent Developments in Parkinson's Disease. Florham Park, NY: Macmillan Healthcare Information, 1987:153–163.
25. Lang AE, Fahn S. Assessment of Parkinson's disease. In: Munsat T, ed. Quantification of Neurologic Deficit. Boston: Butterworth, 1989:285–309.
26. Schwab R, England A. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham F, Donaldson I, eds. Third Symposium on Parkinson's Disease. Edinburgh: E&S Livingstone, 1969:152–157.
27. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427–442.
28. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
29. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;17:37–49.
30. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry 1968;114:797–811.
31. Pankratz N, Nichols WC, Uniacke SK, et al. Genome screen to identify susceptibility genes for Parkinson disease in a sample without parkin mutations. Am J Hum Genet 2002;71:124–135.
32. Pankratz N, Nichols WC, Uniacke SK, et al. Genome-wide linkage analysis and evidence of gene-by-gene interactions in a sample of 362 multiplex Parkinson disease families. Hum Mol Genet 2003;12:2599–2608.
33. Pankratz N, Uniacke SK, Halter CA, et al. Genes influencing Parkinson disease onset: replication of PARK3 and identification of novel loci. Neurology 2004;62:1616–1618.
34. Nichols WC, Elsaesser VE, Pankratz N, et al. LRRK2 mutation analysis in Parkinson disease families with evidence of linkage to PARK8. Neurology 2007;69:1737–1744.
35. Nichols WC, Pankratz N, Hernandez D, et al. Genetic screening for a single common LRRK2 mutation in familial Parkinson's disease. Lancet 2005;365:410–412.

Effect of aerobic training in patients with spinal and bulbar muscular atrophy (Kennedy disease)

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ABSTRACT

Objective: We examined the effect of aerobic exercise in patients with spinal and bulbar muscular atrophy (SBMA). SBMA is caused by a defect androgen receptor. This defect causes motor neuron death, but considering the important function of androgens in muscle, it is possible that muscle damage in SBMA also occurs independently of motor neuron damage.

Methods: Eight patients with SBMA engaged in regular cycling exercise for 12 weeks. Maximum oxygen uptake ($V_{O_{2max}}$), maximal work capacity (W_{max}), muscle morphology, citrate synthase (CS) activity, body composition, EMG, static strength measurements, lung function, plasma proteins, and hormones were evaluated before and after training. Evaluation of improvements in activities of daily living (ADL) was conducted after training.

Results: W_{max} increased by 18%, and CS activity increased by 35%. There was no significant change in $V_{O_{2max}}$ or any of the other variables examined before and after training, and the patients with SBMA did not feel improvements in ADL.

Conclusions: Frequent, moderate-intensity aerobic conditioning is of little beneficial effect in patients with spinal and bulbar muscular atrophy (SBMA). High levels of plasma creatine kinase and muscle regeneration indicate a primary myopathic affection, which, in parallel with the motor neuron deficiency, may attenuate the response to exercise training in patients with SBMA.
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GLOSSARY

ADL = activities of daily living; **AR** = androgen receptor; **ASI** = androgen sensitivity index; **BMI** = body mass index; **CK** = creatine kinase; **CS** = citrate synthase; **FSH** = follicle-stimulating hormone; **LH** = luteinizing hormone; **MU** = motor unit; **SBMA** = spinal and bulbar muscular atrophy; **Vo_{2max}** = maximum oxygen uptake; **W_{max}** = maximal work capacity.

Spinal and bulbar muscular atrophy (SBMA), also know as Kennedy disease,[1] is caused by a CAG-repeat expansion (range 38–62 repeats) in the gene on the X chromosome, encoding the androgen receptor (AR).[2-4] The AR is believed to influence the expression of a large variety of genes by acting as a transcription factor. When testosterone or dihydrotestosterone binds to the AR, the AR–ligand complex binds to the target gene and regulates its expression.[5] SBMA is primarily believed to be a neuronopathy, caused by a toxic gain of function of the AR when associated with testosterone.[5] This is supported by the fact that only men express this characteristic phenotype, although heterozygous and homozygous females may have some symptoms.[6,7] SBMA is a slowly progressive disease, with age at onset of muscle weakness in the third to sixth decade of life. Clinically, the patients experience weakness, atrophy, and fasciculations in the muscles of the extremities and of the bulbar and facial muscles. The dysfunctional AR renders patients partially androgen insensitive, with an increased androgen sensitivity index (ASI) and gynecomasty.[8] A potential primary effect of dysfunctional AR on muscle itself has been

Supplemental data at www.neurology.org

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Table Demographic data on eight patients with spinal and bulbar muscular atrophy

Patient no.	Age, y	BMI, kg/m^2	No. of CAG repeats	Gynecomastia	Medication
1	63	21	45	No	None
2	56	25	46	Yes	Sildenafil 25 mg/wk + calcium tablet 1/d
3	53	23	52	Yes	Fluoxetine 20 mg/d + pantoprazole 20 mg 1–2/mo
4	49	22	44	No	None
5	59	27	42	No	Calcium tablet 1/d
6	58	18	45	Yes	Testosterone undecanoate 40 mg/d
7	61	26	45	Yes	Bendroflumethiazide/KCl 1/d + atenolol 25 mg/d + carbimazole 5 mg/d + zolpidem 5 mg/d
8	51	27	42	Yes	None
Mean ± SD	56 ± 5	24 ± 3	45 ± 3	—	—

Patient 6 continued treatment with testosterone after a clinical trial of testosterone, where he felt better while taking the drug.
BMI = body mass index.

given little attention in SBMA, although it is well established that androgens have an important anabolic function in skeletal muscle.[9]

There is no specific treatment for SBMA. We have successfully implemented cycle exercise programs to treat patients with muscular dystrophies and metabolic myopathies. All of these patients improved their maximum oxygen uptake ($V_{O_{2max}}$) and maximal work capacity (W_{max}) with training and subjectively felt improvement in activities of daily living (ADL), and the training was well tolerated and never induced muscle damage.[10-14] Most of these patients share clinical characteristics of patients with SBMA, such as muscle weakness and wasting and sedentary lifestyles.

We studied the effect of aerobic training for 3 months in eight patients with SBMA.

METHODS

Subjects. Inclusion criteria for participation in this study were 1) confirmed diagnosis of SBMA by DNA analysis, 2) age between 18 and 65 years, 3) capability of uninterrupted cycling for at least 20 minutes, and 4) completion of 70% of the planned exercise sessions. Exclusion criteria were 1) other serious medical conditions, 2) regular exercise training of more than 1 hour per week, and 3) inability to cooperate mentally. Based on the predicted treatment response and variability in training effects, it was calculated that a minimum of seven patients was needed to provide enough power to the study (appendix e-1 on the *Neurology*® Web site at www.neurology.org). Eleven patients were originally selected for the study. One patient (age 63 years, body mass index [BMI] 33 kg/m^2, 46 CAG repeats) was wheelchair bound and could only walk a few meters with assistance. He could only cycle for 3 minutes at a resistance of 20 watts, the lowest possible resistance on the cycle-ergometer, and was therefore excluded. Two other patients were excluded because they completed less than 70% of the planned exercise sessions. One of these patients (age 59 years, BMI 30 kg/m^2, 42 CAG repeats) never started the exercise protocol, because of illness in his close family. The other patient (age 49 years, BMI 20 kg/m^2, 47 CAG repeats) had completed just 16 of 42 sessions after 3 months. The low compliance was due to lack of motivation. Data in this study are shown for the remaining eight patients with SBMA, all of whom completed the study. DNA analyses confirmed the diagnosis in each patient (see the table for demographic data).

The study was approved by The Committee on Biomedical Research Ethics of the Capital Region of Denmark (project ID: H-KF-01 297836 KF). All the participants received written and oral information about the experiment and potential risks and gave informed consent to participate.

Experimental protocol. ***Pre-experimental evaluations.*** The patients were instructed to work for 12 weeks on a stationary cycle-ergometer at home. They were equipped with a Polar pulse watch and transmitter. Before training was started, an incremental exercise test was conducted to assess the maximal oxidative capacity of the patients. The patients were tested in the postabsorptive state on a cycle-ergometer (T6, Tunturi, Finland). Pulmonary gas exchanges were evaluated with a gas analyzer/flowmeter (Quark b^2, Cosmed, Italy). Heart rate was monitored continuously with pulse watches and a three-lead electrocardiogram. After the max test, the pulse interval corresponding to 65% to 70% of $V_{O_{2max}}$ was identified during cycling at constant workload. Patients were instructed to train at home at this heart rate, and heart rate limits were stored on the pulse watch, thus providing patients auditory feedback if limits were violated during training. Patients trained 30 minutes per session and were instructed to adjust workload according to the target heart rate.

Each training session at home was recorded on the pulse watch. These data were downloaded on a computer and analyzed with Polar ProTrainer 5 software (version 5.20.132), enabling us to view precise recordings of heart rate and of time and duration of training for each training session. Data from each patient were analyzed to validate frequency and compliance to training. The subjects were instructed to gradually increase the training frequency from two training sessions in weeks 1 and 2, to three sessions in weeks 3 and 4, and then to five sessions per week in the remaining eight weeks.

Endpoints, efficacy, and safety evaluations. Changes in $V_{O_{2max}}$, W_{max}, and ADL with training were defined as primary