LETTERS TO THE EDITOR

**18F-Dopa vs Dopamine Transporter Ligands in Positron Emission Tomographic and Single-Photon Emission Computed Tomographic Scans for Parkinson Disease**

We read with interest the article by Ribeiro et al.1 Although the 18F-dopa positron emission tomographic (PET) scan is the current imaging gold standard for the diagnosis of early Parkinson disease (PD) and for measuring disease progression in clinical trials, the authors concluded that the ligand, 76Br-FE-CBT, that binds to the dopamine transporter (DAT) may be more suitable for detecting cases of early PD and assessing disease progression than 18F-dopa. This is because 18F-dopa uptake depends not only on the density of dopaminergic terminals in the striatum but also on dopamine turnover, which may be compensatorily increased in early PD.2,3 Thus, 18F-dopa uptake might overestimate the number of striatal dopaminergic nerve terminals in these patients.

In support of this theory, we recently described 2 patients who had typical early PD, both with unilateral rest tremor, bradykinesia, and rigidity. They had a positive response to dopamine agonists and underwent 18F-dopa PET and [123I]-alatropane single-photon emission computed tomographic (SPECT) scans within 3 months.4 Like β-CIT and 18Br-FE-CBT, alatropane when radiolabeled becomes a ligand that specifically binds to the DAT. In these 2 patients, both PET scans were nondiagnostic, but their SPECT scans showed clear, unilateral striatal reduction of tracer uptake contralateral to their parkinsonian side.

Recently, a double-blind 18F-dopa PET study was conducted that compared disease progression among patients with early, untreated PD who were given ropinirole hydrochloride or levodopa.5 Of 186 subjects, 11% were excluded from the primary analysis because of “normal” striatal 18F-dopa uptake on their baseline PET scans. Consequently, reporting and following cases of PD that demonstrate normal findings on 18F-dopa PET scans and abnormal results on examinations using DAT ligands is of major interest.

Some of us were investigators for the REAL-PET Study,2 which measured the progression of Parkinson disease for 2 years using 18F-dopa in patients blindly assigned to treatment with ropinirole hydrochloride or levodopa. We cannot comment on this study because the data are still unpublished. However, the subjects with normal 18F-dopa PET scan findings at baseline who were excluded from the analysis also had normal PET scan results after 2 years of follow-up, which is very unlikely in patients with PD. Moreover, the caudate-putamen ratio in these subjects was normally high considering the usual pattern of dopaminergic denervation in PD.6 Unfortunately, it is possible that the PET scan analysis revealed misdiagnosis in these subjects. However, we recommend that our colleagues refer directly to the published data when available.

We thank Fernandez and Friedman for their comments. Although the results they mention were obtained in a small number of subjects, they point out an unresolved question: whether patients with PD can have normal findings on 18F-dopa PET scans. From our results, one could extrapolate that the compensatory increase of the dopa decarboxylase might produce normal 18F-dopa PET scan findings despite the disappearance of 20% or 30% of the dopaminergic neurons. However, the study showing that 18F-dopa uptake is highly correlated to motor function suggests that when this uptake is normal, the motor performance is nearly normal. Finally, abnormal results on 18F-dopa PET scans have occurred in asymptomatic co-twins of patients with PD.7 Although this type of PD is probably genetic and may be different from the idiopathic form, this finding argues against the likelihood of PD symptoms without abnormal 18F-dopa PET scan findings. Finally, technical parameters for image acquisition and analysis might influence the ability to discriminate between normal and abnormal results on these scans.

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A Null Mutation in the CNTF Gene Is Not Associated With Early Onset of Multiple Sclerosis

In a previous ARCHIVES article, Giess et al\(^1\) reported an association of a null mutation in the CNTF gene with early onset of multiple sclerosis (MS). Because CNTF has myeloprotective and survival-promoting effects on neuronal cells, homozygosity for the null mutation (−/− genotype) may affect disease outcome. The authors identified 7 (2.4%) of 288 patients with MS as carriers of this genotype. These patients had a significantly earlier onset of the disease (median, 17.0 years; 25th percentile, 16.3 years; 75th percentile, 24.0 years) compared with patients carrying at least 1 functional CNTF allele (median, 27.0 years; 25th percentile, 22.0 years; 75th percentile, 33.0 years; \(P = .007\) using the Mann-Whitney test).

We recently reported finding homozygosity for the null mutation in 10 (2.9%) of 349 patients with MS as compared with 8 (1.8%) of 434 healthy controls.\(^2\) There was no significant correlation between the CNTF genotype and age at onset, clinical course, or severity of MS. We have now reanalyzed our data to directly compare our results with those published by Giess and colleagues. In our study, patients homozygous for the null mutation had no earlier onset of the disease (median, 28.0 years; 25th percentile, 22.5 years; 75th percentile, 30.5 years) than patients carrying 1 functional CNTF allele (median, 28.0 years; 25th percentile, 22.0 years; 75th percentile, 35.0 years; \(P = .74\) using the Mann-Whitney test) or 2 functional CNTF alleles (median, 29.0 years; 25th percentile, 22.0 years; 75th percentile, 35.0 years; \(P = .74\) using the Mann-Whitney test).

Even though CNTF might appear to be a promising disease-modifying gene, our data do not confirm the results described by Giess and colleagues. We suggest that the requirement for CNTF in myelogenesis or cell survival may be bypassed by the presence of a second ligand or the redundancy of functional activity of other complementary neurotrophic factors.

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In reply

In the study by Hoffmann et al\(^1\), CNTF genotypes in 349 patients with MS and 434 healthy controls were examined.

This study confirms some of our results. The authors also detected no differences between allelic frequencies in patients with MS and controls, indicating that the CNTF null mutation is not a risk factor for the development of MS. As mentioned in their letter, the authors apparently could not find any association between the CNTF genotype and the MS course or disease severity.

In their initial analysis, Hoffmann and colleagues could not detect any difference between CNTF genotypes in regard to the onset of clinical symptoms. The authors compared patients carrying 2 functional CNTF alleles (CNTF +/+ ) with patients carrying 1 functional CNTF allele (CNTF +/− ). Their negative results are not surprising because patients heterozygous for the CNTF null mutation are expected to produce sufficient amounts of CNTF.\(^3\) In their additional analysis in which they extended the genetic comparisons according to our study, they still did not find an earlier disease onset in patients with the CNTF −/− genotype. In this context, it would be important to know how the clinical data were ascertained (eg, medical record review or confirmation of the clinical disease onset by personal contact with patients); our patients were tracked within prospective protocols for many years using highly standardized conditions.

This controversy underlines the problem of clinical genetic studies with small groups of patients. In our opinion, studies of this kind are reasonable for the generation of new hypotheses that later need to be tested vigorously in large population studies.

There are 3 principal types of bias that could account for controversial results: (1) ascertainment bias, or selection of clinical subtypes based on differences in referral; (2) low allele frequency of suspected candidate genes, which may induce bias when small differences in the observed population are statistically significant yet disappear with larger studies; and (3) disease heterogeneity, which may cause bias by including an unknown distribution of histopathological subtypes.\(^3\)

The strongest argument in favor of our observation comes from our recently published experimental studies, in which we observed a more severe and more chronic course of myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis in CNTF-deficient mice compared with wild-type C57BL/6 mice.\(^4\) Animals with the CNTF −/− genotype also exhibited a significantly earlier disease onset than wild-type mice. Histopathological analysis showed a more severe dystrophy of myelin and worse axonal damage in CNTF-deficient mice. From the animal study, we conclude that CNTF is likely to modulate glial cell survival in an inflammatory environment.

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Cerebrotendinous Xanthomatosis:
Juvenile Cataract and Chronic Diarrhea
Before the Onset of Neurologic Disease

In the April issue of the ARCHIVES, Moghadasian et al. published a mini-review dealing with a new appraisal of cerebrotendinous xanthomatosis (CTX). Concerning the diverse manifestations of this potentially treatable disease, the authors stressed that the association of bilateral juvenile cataracts with chronic diarrhea may represent the earliest clinical manifestation of CTX and that unexplained bilateral cataracts with chronic diarrhea are the features that suggest this diagnosis before the onset of neurologic disease. I fully agree with these statements but would like to add the references of the studies in which these conclusions were made. Furthermore, I believe that cerebrotendinous xanthomatosis should not be considered a rare disease. Of all our patients with a known neurologic disorder occurring with early-onset cataracts, those with CTX make up the second largest group after myotonic dystrophy.

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Correction

Error in Figure. In the Original Contribution titled “Effects of Coenzyme Q10 in Early Parkinson Disease,” published in the October issue of the ARCHIVES (2002;59:1541-1550), there was an error in Figure 1. In the group that received 600 mg/d, 6 patients completed 16 months without needing levodopa. Figure 1 is reprinted correctly here.

Figure 1. Patient flowchart.