Iron Accumulation in the Substantia Nigra of Patients With Alzheimer Disease and Parkinsonism

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Background: Preliminary studies have shown an increase in iron accumulation in the substantia nigra but not in the hippocampus in patients with Parkinson disease without dementia and the reverse in patients with Alzheimer disease (AD) and no parkinsonism.

Objective: To determine whether iron levels (measured as T2 shortening on magnetic resonance images) are greater in the substantia nigra of patients with AD who have parkinsonism than in those with AD alone.

Design: Case-control study.

Setting: Albany Medical College, Albany, New York.

Participants: Fifteen patients with only AD (controls) and 18 with AD as well as parkinsonism, aged 56 to 89 years, and with a total Clinical Dementia Rating of 5.0 to 11.5. Patients were selected according to the purity of their disease; patients with a Unified Parkinson’s Disease Rating Scale motor score of 15 or greater were considered to have parkinsonism.

Main Outcome Measure: Area under the curve for short T2 (30 milliseconds) in patients with only AD vs patients with AD who developed parkinsonism.

Results: Patients who developed parkinsonism along with their existing dementia had significantly more iron in their substantia nigra than did patients with AD alone (P = .03, 2-sample t test).

Conclusions: Iron accumulation may be a predictor of parkinsonism. The development of parkinsonism during the course of AD appears to be associated with the accumulation of iron, which in turn may contribute to the pathogenesis of neurologic decline.


METHODS

Fifteen patients with AD (control group) and 18 with both AD and parkinsonism were selected for this study according to the purity of their disease (no other confounding neurodegenerative disease). The age of the patients was normalized between the 2 groups; ages ranged...
from 66 to 86 years, with a mean of 75.0 years in the AD group and 76.9 in the AD with parkinsonism group, and a median of 75.0 and 78.5 years, respectively. Informed consent was obtained from each subject or from his or her medical representative. Parkinsonism was diagnosed by means of the Unified Parkinson’s Disease Rating Scale (UPDRS). The UPDRS motor scores are commonly used for assessing the degree of parkinsonism in a patient. Patients with a UPDRS motor score of 15 or greater were considered to have moderate to severe parkinsonism. The diagnosis of AD was made according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association criteria for AD. The severity of the disease was determined by means of the Clinical Dementia Rating. The sum of the 6 boxes on this test was used to ensure that the groups were at the same stage of this disease. For both groups, the mean of the sum of the boxes was 7.8, and the scores ranged from 1 to 18. All subjects in both groups underwent MR imaging within 1 month of their disease diagnosis to ensure that the disease would not have progressed substantially between the time of diagnosis and the time of imaging.

A 3-T whole-body MR imager (GE Healthcare, Waukesha, Wisconsin) with a birdcage head coil was used to image the brains of all of the patients as previously described. The substantia nigra was manually segmented on each of the coronal MR images in which it was present (Figure 1). High-resolution brain atlases were used as templates for anatomic boundaries when this segmentation was performed. Both the left and right substantia nigra were segmented separately but were treated together as a unit. Iron deposits have been shown to shorten T2 relaxation times on T2-weighted MR images, so the fraction of voxels below a short T2 cutoff value will correspond to the amount of iron in that specific region of the brain. The exact cutoff value has been arbitrarily determined as 30 milliseconds. The T2-weighted images were used to segment the substantia nigra because these images provide a good contrast between the substantia nigra, which has a short T2 (high iron content), and the neighboring regions with intermediate to high T2 (lower iron content), such as white and gray matter.

For each subject, histograms of the T2 distribution times were generated for the substantia nigra region by means of the Analysis of Functional Neuroimages, which is a standard software program used to both segment brain regions and calculate T2 histograms of MR images. The short T2 values, corresponding to the left-hand tail of the histogram, represent regions of increased iron concentration. Therefore, the area under the curve for a T2 value of 30 milliseconds was calculated. Differences between means were analyzed via a 1-tailed t test. Significance was set at $P < .05$. The results are presented as the mean (SD).

**RESULTS**

The fraction of voxels with a T2 less than 30 milliseconds was calculated for both the control group and the group with AD and parkinsonism. For the group with only AD, the mean (SD) was 0.071 (0.069), whereas for the group who had AD with concurrent parkinsonism, the mean was 0.120 (0.071). This difference was statistically significant ($P = .03$). This finding, in turn, suggests a significantly greater amount of iron in this region of the brain for the group with AD and parkinsonism than for the group with only AD.

The entire averaged T2 histogram for the control group and the group with parkinsonism (Figure 2) shows that the group that had parkinsonism had a significantly greater frequency of voxels at the lower T2 times. The mean T2 time for the group with only AD was 44.98 (11.41) milliseconds, whereas the mean T2 time for the group with AD and concurrent parkinsonism was 38.45 (5.82) milliseconds. This difference was significant ($P = .03$). These lower T2 times correspond to increased iron accumulation, so the significant increase in the frequency of voxels at these low T2 values indicates a greater amount of iron accumulation in the group exhibiting parkinsonism.
It has been shown that the number of voxels calculated in a specific brain region is a valid measure of the actual volume of that region and can be used to determine shrinkage or enlargement of a certain region.\textsuperscript{17,18} Therefore, the number of voxels in the entire substantia nigra was also calculated for both groups to rule out the possibility of a change in the volume of the nigra due to the development of parkinsonism. The mean number of voxels for the group with only AD was 682.5, and the mean number of voxels for the group that developed parkinsonism was 683.0. This difference was not statistically significant (P = .27). This indicates that the change between the 2 groups in the number of voxels at low T2 values cannot be attributed to a shrinkage of the substantia nigra.

Iron is associated with the substantia nigra in patients with AD who develop parkinsonism. Previous studies showed an increase in the amount of iron in the substantia nigra of patients with Parkinson disease compared with patients with AD without parkinsonism,\textsuperscript{2} and our study now fills the remaining gap in truly understanding this severely impairing combination of diseases. Alzheimer disease with parkinsonism may be confused clinically with dementia with Lewy bodies (DLB). Dementia with Lewy bodies is characterized by fluctuating cognition, parkinsonism, and visual hallucinations;\textsuperscript{19-22} however, the literature varies in how many of these clinical symptoms must be met for DLB to be diagnosed. One source explains that 2 of these 3 symptoms must present to make the diagnosis of DLB,\textsuperscript{20} whereas another states that, of these 3 core clinical features, the only one that can be used to differentially diagnose DLB is visual hallucinations and that the combination of parkinsonian symptoms along with AD is not in itself diagnostic of DLB.\textsuperscript{21} Yet another source provides evidence that fluctuating cognition is significantly more prevalent in patients with DLB than in patients with AD.\textsuperscript{22} However, regardless of which definition is used to diagnose DLB, none of our patients with AD and parkinsonism fit the criteria for DLB. Using the sum of the boxes on the Clinical Dementia Rating, scores on the Mini-Mental State Examination, and clinical evaluations, we were able to determine that our patients with AD and parkinsonism did not have fluctuating cognition, but instead had an even, progressive decline in cognitive function. Furthermore, none of our patients experienced visual hallucinations.

Another diagnosis that may be confused with AD and parkinsonism is Parkinson disease with dementia, which defines a disorder that starts with Parkinson disease and later manifests a slow progression of dementia.\textsuperscript{20} Our patients started out with AD and later began showing parkinsonian symptoms, and therefore the diagnosis of Parkinson disease with dementia does not apply.

Iron may play a role in the pathogenesis of parkinsonism in AD and in the rapid decline of AD with parkinsonism. Iron accumulation may be a predictor of parkinsonism and more rapid decline earlier in the course of the disease before the parkinsonism develops. It would be ideal to longitudinally measure the iron levels of individual patients at different stages of their progression through parkinsonian symptoms, which potentially could show a direct cause between iron and the rapid decline of symptoms. Now that this correlation has been drawn, early intervention may be implemented to lessen the symptoms of the disease, increase the effectiveness of the few treatments that exist, decrease the need for aggressive therapies, and possibly prevent this disease.\textsuperscript{23} This study was cross-sectional because of limited longitudinal data. Future studies of parkinsonism in the course of the progression of AD showing increases in iron in association with changes in the UPDRS would be even more convincing evidence of a causative role for iron and might serve as a potential biomarker to evaluate a therapeutic intervention.

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